EPIDEMIOLOGY OF BREAST CANCER: RISK FACTORS, TREATMENT ADHERENCE AND OUTCOME OF BREAST CANCER PATIENTS ATTENDING TIKUR ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA

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DISSERTATION FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD) IN PUBLIC HEALTH

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Internal Examiner **Signature and Date**

List of original papers

This thesis is based on the following papers which will be referred to in the text by their Roman numbers (I- V).

Paper I. Fatuma Hassen, Fikre Enquselassie, Ahmed Ali, Adamu Addissie, Girma Taye, Mathewos Assefa' Aster Tsegaye. Socio-demographic and hematological determinants of breast cancer in a tertiary health care and teaching Hospital in Addis Ababa, Ethiopia **Ethiop. J. Health Dev. 2021; 35(2)**

Paper II. Fatuma Hassen, Fikre Enquselassie, Ahmed Ali, Adamu Addissie, Girma Taye, Mathewos Assefa' Aster Tsegaye. Profile and association of ABO/Rh blood group with breast cancer at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: Case case-control study **(Manuscript), ready for publication**

Paper III. Fatuma Hassen, Fikre Enquselassie , Ahmed Ali, Adamu Addissie, Girma Taye, Mathewos Assefa' Aster Tsegaye. Risk Factors associated with Breast Cancer among Patients Treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: Case case-control study **BMJ Open 2022; 12:e060636**.

Paper IV. Fatuma Hassen, Fikre Enquselassie , Ahmed Ali, Adamu Addissie, Girma Taye, Mathewos Assefa' Aster Tsegaye. Chemotherapy, treatment adherence, and associated factors among breast cancer patients treated at Tikur Anbessa Specialized and Teaching Hospital Asian **Pac J Cancer Prev, 23 (9), 3035–3041.**

Paper V. Fatuma Hassen, Fikre Enquselassie, Ahmed Ali, Adamu Addissie, Girma Taye, Mathewos Assefa' Aster Tsegaye Survival of breast cancer patients treated at Tikur Anbessa Specialized and Teaching Hospital, **(Manuscript), ready for publication**

List of Abbreviations and Acronyms

AACR	Addis Ababa Cancer Registration
ABO	Classification of human blood based on the inherited properties of red blood cells consisting of A, B, AB, and O types
AI	Aromatic Inhebitor
AIDS	Acquired Immunodeficiency Syndrome
AOR	Adjusted Odds Ratio
ASDR	Age Standardized Death Rate
BC	Breat cancer
BMI	Body Mass Index
BRCA1	BReast Cancer gen 1
BRCA2	BReast Cancer gen 2
BCSS	Breast Cancer specific Survival
CDR	Crude Death Rate
COR	Crude Odds Ratio
CT	Computed Tomography
DHS	Demographic and Health Surveys
DFS	Disease Free Survival
DLNM	Distant Lymph Node Metastases
DNA	Deoxyribonucliec acid
EML	Essential Medicines List

ER	Estrogen Recepter
EU	European Union
FBC	Female Breast Cancer
FNA	Fine Needle Aspitation
GBD	Global Burden of Disease
HER 2	Human epidermal growth factor receptor 2
HB	Hemoglobin
HR	Hazard Ratio
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
HDI	Human Development Index
INCTR	International Network for Cancer Treatment and Research
ISLM	Ipsilateral Suprac Lavicular Lymph node Metastases
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Cell Volume
MFS	Metastesized Free Survival
MPV	Mean Platelet Volume
MRI	Magnetic Resonance Imaging
NGO	Non-Governmental Organization
OR	Odds Ratio

PCV	Packed Cell Volume
PDA	Particle Distribution Analysis
PR	Progesterone Receptors
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
SD	Standard Deviation
SoM	School of Medicine
SPH	School of Public Health
SPSS	Statistical Package for Social Sciences
SSA	Sub-Saharan Africa
TASH	Tikur Anbessa Specialized Hospital
USA	United States of America
WBC	White Blood Cell
WHO	World Health Organization

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Abstract

Background: Breast cancer is the most common cancer and the leading cause of cancer deaths among women worldwide. In resource-limited nations, the combination of late presentation, low survival rates, a poor health care system, and a lack of health care financing resource contribute to the population's perception that treatments for breast cancer are ineffective or unavailable, thereby causing more delay in diagnosis and treatment. Adherence has been identified as a primary determinant of patient outcome and clinical benefit. In Ethiopia, breast cancer is one of the most commonly diagnosed cancers among women. However, due to constrained health resources and poor awareness among the population, most patients did not visit health facilities for early diagnosis and treatment. As a result, most patients did not benefit from treatment since most Ethiopian women are frequently diagnosed at an advanced stage. Moreover, non-adherence to chemotherapy is not well investigated in patients attending their treatment in Addis Ababa, Ethiopia.

Objective: The objective of the study was to assess the epidemiology of breast cancer among patients treated at the Oncology Department, Tikur Anbessa Specialized Hospital, and Addis Ababa, Ethiopia.

Methods: The study applied multiple epidemiologic designs. A case-control study was conducted from May 2018 to June 2019. A total of 230 cases and 230 controls (care givers) participated in order to assess the sociodemographic and hematologic profiles and risk factors for breast cancer. The cross-sectional study was conducted among 164 breast cancer patients taking chemotherapy. In addition, secondary data were also collected to assess the outcome of breast cancer patients treated from September 2010 to August 2014 at TASH. Data were collected using face-to-face interviews, chart reviews, and telephone interviews. An independent student t-test was performed to compare the mean hematological parameters. A chi-square test was done to see if there was a significant difference in hematologic parameters between cases and controls. A binary logistic regression analysis was conducted to examine the association between potential risk factors and breast cancer. A multivariable logistic regression model-based analysis was conducted to control the effect of potential confounding factors. Median ages at diagnosis and the interquartile range (IQR) were calculated. Based on life table analysis, one-, three-, five-, and 10-year overall survival rates were calculated. Median survival estimates were obtained using the

Kaplan-Meier survival analysis method. Survival curves were compared using the log-rank statistic. Cox's proportional hazards model was used for bivariate and multivariable analyses.

Results: The mean (± SD) ages of study patients for the case-control study were 42.8 (±12.1) and 39.3 (±11.1) years for cases and controls (caregivers of cancer patients), respectively. Nearly half, or 100 (43.5%) of patients and 34 (14.8%) of controls, did not have any formal education. Moreover, the majority, 175 (76.1%) of cases and 155 (67.4%) of controls, were married. The mean values of most hematological parameters were significantly lower among cases. Moreover, the mean platelet count was higher among cases. However, there was no significant difference in the total white cell count among cases and controls. On the other hand, nearly half, 89 (46.6%) cases and 96 (41.7%) controls, were blood group O. Blood group AB was the least common, accounting for 19 (9.9%) and 20 (8.7%) of the cases and controls, respectively. However, a statistically significant association was not found between breast cancer and the ABO or Rh blood type.

Based on risk factor analysis, the odds of breast cancer were higher among illiterate women (AOR: 2.57; 95% CI: 1.38–4.99) and among those who were unemployed (AOR: 3.78; 95% CI: 1.46–9.78; P = 0.006) as compared to educated and employed women. However, the odds of breast cancer were 0.19 times lower among pre-obese women (AOR. 0.19(95%CI: 0.19; 95% CI: 0.043–0.826) compared to underweight women. Based on factors related to life style, consumption of oil solid at room temperature was associated with breast cancer (AOR: 3.50, 95% CI: 2.18–5.62, P<0.001). In addition, women who used animal dung or wood as a source of fuel had higher odds of breast cancer (AOR: 4.91, 95% CI: 2.72–8.86, P<0.001) compared to women who used electricity as a source of fuel. Moreover, women who had previous benign surgery, post-menopausal women, and women with early menarche (<12 years) had significantly higher odds of breast cancer as compared to women who had no previous benign surgery, premenopausal women, and menarche >15 years, respectively. While women who had moderate physical activities had significantly lower odds of breast cancer as compared to women who had no moderate physical activities, In the study that investigates adherence to chemotherapy, among 164 breast cancer patients, 137 (83.5%) were adherent to their chemotherapy. Severe illness was one of the main reasons for non-adherence. Distance from the referral center and types of

recommended treatment regimens were significantly associated with non-adherence. For survival analysis, our retrospective cohort study included a total of 402 patients, with a median [IQR] age at diagnosis of patients 43[35–50] years. The median follow-up time was 58.3 months. By the end of follow-up, 233 (58%) of the patients were dead. The five- and ten-year survival rates were 50% and 34%, respectively. Based on multivariable cox regression analysis, advanced stage at diagnosis (HR = 3.84; 95% CI 2.00–7.35, P< 0.001) and cancer metastasized tumor 1.79 (95% CI 1.13-2.83, P = 0.012) were significantly associated with a higher risk of death.

Conclusion and recommendations: Based on the findings of the case-control study, illiterate women had higher odds of breast cancer. As compared to controls, the majority of the hematological profiles of patients were significantly lower. The study demonstrated there was no significant association between the ABO/Rh blood group and breast cancer. The result of the risk factors for breast cancer revealed that occupational status, using wood or animal dung as a source of fuel, consumption of solid oil, menopausal status, early menarche, and previous benign breast surgery were linked with breast cancer. While women with a history of moderate physical exercise had lower odds of breast cancer. Regarding level of adherence, good adherence to chemotherapy was observed among 137 (83.5%). The most identified factor for non-adherence was the severity of the illness. The study also indicated a relatively poor survival rate, which was associated with a late-stage diagnosis and metastasizing cancer. Based on the findings, we recommend that attention be given to high-risk breast cancer groups and those with designated hematologic abnormalities. Efforts should be exerted for further study with a large sample size in order to establish the purpose of the ABO blood group in the prognosis of breast cancer. There is also a need to design applicable interventions to inform women about lifestyle changes to decrease breast cancer risk in high-risk groups. Since distance, transportation cost, and access to health care are the most important factors that determine adherence to chemotherapy, the extension of cancer screening and treatment centers should be encouraged. Moreover, there is a need for strengthening public awareness and mass screening to enhance early initiation of treatment, reduce advanced stages, and improve the survival of patients.

Key words: Breast cancer, hematological profiles, risk factors, adherence, survival

1. Introduction

1.1. Background

Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably beyond their usual boundaries to invade adjoining parts of the body and other organs. The majority of breast cancers begin in the parts of the breast tissue that are made up of glands, or lobules, and ducts that connect the lobules to the nipple. Although we generally refer to breast cancer as a single disease, it is distinguished by up to 21 distinct histological subtypes and at least four different molecular subtypes [1–3].

Breast cancer is the primary cause of cancer-related deaths in women worldwide. In 2020, there were 2.3 million new cases of breast cancer, or 24.5% of all cancer cases, and 685,000 cancer fatalities, or 15.5% of all cancer fatalities [4]. Between nations, there are differences in the prevalence and mortality of breast cancer. Belgium (112.3 per 100,000 people) had the highest age-standardized incidence rate. Although Iran (35.8 per 100,000 people) has the lowest incidence [4], female breast cancer (FBC) now accounts for a greater proportion of new cases of cancer than lung cancer globally [5].

According to a study, the trend for breast cancer fatalities is rising globally. In 1990, about 344.9 thousand people lost their lives to breast cancer. However, in 2017 [6], this number rose to 600.7 thousand. Between 1990 and 2017, most African and South Asian countries experienced a significant increase in the age-specific mortality rate (ASMR) of FBC. The greatest increase was found in Zimbabwe, followed by Mauritius and Lesotho. In contrast, most European countries and the Americas experienced a significant decrease in the ASMR of FBC [6]. Data from 10 out of the 11 cancer registry networks in Africa showed that there was an increasing incidence rate of breast cancer in all registries (except in Nairobi). In this network, which includes countries representing each of the four sub-Saharan African regions, the cumulative risk varied in different countries. In such cases, the highest incidence rates were observed in Mauritius, Nairobi, Kenya, and the Seychelles [7].

The risk of breast cancer can be increased by a number of variables. Despite the fact that their precise contributions are still being determined, factors including lifestyle, particularly urbanization, a Westernized diet, and likely rising awareness have been raised as potential

contributors [8]. Some risk factors for breast cancer are things that cannot change, such as being female, getting older, having certain breast conditions, having a family history of breast cancer, or inheriting certain gene changes. There are factors that contribute to the risk of breast cancer, including obesity, harmful use of alcohol, genetic mutation, history of radiation exposure, and reproductive history [9]. Approximately half of breast cancers develop in women who have no identifiable breast cancer risk factors other than being female and old age [9, 10].

The effectiveness of preventive and screening programs depends on the economic conditions of the country. Sensitive, specific, easily available, and cost-effective diagnostic and therapeutic approaches are urgently required for the reduction of breast cancer incidence and prevalence [11]. In high-income countries, breast cancer has a good prognosis, but in sub-Saharan Africa (SSA), survival is considerably lower [12]. There is wide variation in the survival rate of breast cancer between different countries. Five-year survival of breast cancer patients ranges from more than 90% in developing countries to 66% in India and 40% in South Africa. Early detection and treatment have proven successful in developing countries and should be applied in developing countries. The great majority of drugs used for breast cancer are already on the WHO Essential Medicines List (EML) [11].

In SSA, 5-year survival is about 50%, i.e., 1 in 2 women diagnosed with the disease have died within 5 years after diagnosis [12]. In sub-Saharan Africa, the proportion of women diagnosed with late-stage (stage III or IV) disease varies substantially between countries. In general, 50% to 90% of breast cancer patients are diagnosed with a regional or metastatic spread of the disease [11]. Advanced stage at diagnosis and lack of access to surgery and systemic therapy, which particularly affect women from lower socioeconomic groups, were the largest contributors to the low rate of survival [12].

In Ethiopia, cancer caused an estimated 50,913.5 (95% CI: 36,092.1–73,018.8) deaths among all age groups and both gender groups in 2016. Death from cancer has also contributed to 18.5% of deaths from non-communicable diseases and 7.3% of the total deaths reported by the same year. The number of deaths from cancer increased by 47.4% between 2000 and 2016 [13].

Thus, the objective of this study was to assess the epidemiology of breast cancer and provide valid evidence in order to inform concerned bodies and policymakers to address issues related to breast cancer, especially problems including exposure to different modifiable risk factors and non-adherence to chemotherapy, which might result in an advanced stage of breast cancer and a poor outcome for patients.

1.2. Statement of the problem

Globally, breast cancer is the top cause of cancer death among women; however, the trend and pattern of the disease vary across different countries [4]. Future incidence predictions indicate that the SSA region will be the place where the majority of the cases and associated deaths will be identified [14]. Even though breast cancer has become an epidemic, a lack of knowledge of symptoms and signs may lead to a delay in seeking treatment among women [15].

Alterations in any of the hematological parameters are the result of the disease progression. A study showed that hematological parameters such as hemoglobin, RBC count, hematocrit, platelet count, and WBC count in breast cancer can be useful guides for monitoring disease progression. Hematological parameters can be advantageous for helping oncologists decide how to provide further treatment [16].

A complete blood count impacts the response of cellular immunity in any cancer patient [17]. Although breast cancer studies reported higher adherence rates than in other non-communicable diseases, non-adherence is still an issue for many breast cancer patients. Based on the study, there is a strong indication of the negative health consequences of non-adherence to early breast cancer systemic treatments. This indicates the need for monitoring patient adherence in the real world and developing strategies to improve it [18].

Cancer control in developing countries is a challenge, considering the economic impact of the disease. Adjuvant endocrine therapy is the standard of care for breast cancer patients with positive hormonal receptors. Adherence to endocrine therapy improves the clinical outcome of disease-free survival (DFS) and reduces medical costs. Improving adherence in developing countries can be achieved by raising awareness among both patients and physicians [19].

Ethiopia is undertaking a fast economic transformation that has increasingly been accompanied by changes in the dietary and lifestyle behaviors of the population, contributing to increasing risks of preventable chronic diseases. In addition, both infectious and non-infectious diseases are a double burden, which is a challenge to health as well as to national socio-economic development [20]. The national STEPs survey conducted in Ethiopia revealed the prevalence of non-communicable disease (NCD) risk factors such as behavioral risk factors (tobacco use, alcohol use, low fruit and vegetable consumption, khat consumption, and physical inactivity) and

biological risk factors (obesity, overweight, high blood pressure, high blood glucose, and abnormal lipids). The majority of the behavioral risk variables were more common among men, according to this study, whereas the biological risk factors were more common among women. [21].

Breast cancer poses a substantial public health threat in Ethiopia [22]. According to a study done in Tikur Anbessa Specialized Hospital, increasing changes in the dietary and lifestyle behaviors of the population are contributing to increasing risks of preventable chronic diseases [20]. In addition, both infectious and non-infectious diseases are the double burden, which is a challenge to the health as well as to the national socio-economic development [20]. Breast cancer poses a substantial public health threat in Ethiopia [22]. According to a study done at Tikur Anbessa Specialized Hospital (TASH), an increase in the trend towards breast cancer cases was observed [23]. Based on cancer registry data for Addis Ababa City, a total of 5,701 cancer cases were registered from September 2011 to August 2014. Based on that data, breast cancer accounted for 33% of cancers among females [24].

In Ethiopia, even though breast cancer is the top cause of morbidity and mortality, extensive delay in diagnosis and a progressive stage at the time of diagnosis are major problems among breast cancer patients [20]. In this regard, a study from two cancer referral centers in Ethiopia found that 71.2% of patients were at an advanced stage at diagnosis [20]. Another study also showed that 88.9% of breast cancer patients had a longer delay [25]. For such a longer delay, the most influential factors were rural residence, illiteracy, and distance from a health facility [20, 25]. In addition to inadequate screening and treatment services, inadequate diagnostic facilities, a poorly structured referral system, financial constraints, and seeking traditional healers and alternative practices were also the main reasons for late diagnosis [20, 25, 26].

In general, cancer contributes 5.8% of total national mortality [26]. However, the trend of breast cancer is increasing, which is the most prevalent kind of cancer in Ethiopia [23]. It is also found that breast cancer poses a significant community health problem in the country [21]. On the other hand, most cancer patients have poor awareness because the majority of patients come for treatment at an advanced stage of the disease [27]. Based on studies in Ethiopia, at the time of diagnosis, more than 70% of patients suffer from advanced and incurable cancers [27, 28].

Since breast cancer is linked to lifestyle, it is important to explore and identify various socio-demographic elements in patients with the disease. This study may help identify the target group for counseling and awareness creation, depending on their needs in the general population. Though breast cancer incidence has increased rapidly in Ethiopia [22], there is still a lack of adequate studies that investigate its epidemiology, sociodemographics, and hematological profile in patients with breast cancer. Therefore, this study was aimed at addressing such gaps at Tikur Anbessa Specialized Hospital, a primary cancer referral and management hospital as well as a teaching hospital in the country.

1.3. Rationale of the study

Breast cancer is a significant public health problem in the Ethiopia [22]. Breast cancer incidence varies by location and is influenced by a variety of factors, including racial, regional, and environmental factors. According to an Iranian study, low latitudes have a higher rate of breast cancer than high latitudes. The results also demonstrated that the risk of breast cancer rose with shorter exposure times and higher intensities at low latitudes [29]. Thus this study will provide valid evidences related to breast cancer associated risk factors in our country situation.

Even though breast cancer incidence has increased rapidly in Ethiopia, there is a lack of adequate studies that investigate risk factors, adherence, and the outcome of breast cancer and are used to design and implement strategies that can be helpful for prevention and improve the outcome of breast cancer patients. Even though many studies found different risk factors [9, 10], for a country like Ethiopia, which has a huge population with different ethnic and geographical variations, lifestyles, and cultural habits, information on breast cancer-associated risk factors is significantly limited. Targeting and supporting these populations to reduce their risk of breast cancer is an essential component of population health.

Patients' adherence to medication has an important role in controlling disease and is key to treatment outcome [18, 19]. However, the situation of patients' adherence is not optimal, despite its importance. Since there are limited studies on chemotherapy adherence and outcome in patients with breast cancer in Ethiopia, this study will provide additional information in order to see how much patient outcome improves or worsens.

In addition, it is vital to assess the hematological status of breast cancer patients at regular intervals during different stages of treatment in order to determine their diagnostic and prognostic values, which can help with better management [16, 17]. It is also found that, besides the controversies and uncertainties surrounding the relationship between ABO and Rh blood types and breast cancer, the most likely mechanism in the progression of an association between blood types and the incidence of breast cancer has not been established yet. Thus, additional evidence from different population groups is needed, and this study will add to the body of literature for future studies assessing the frequency and link of the ABO blood group with breast cancer.

In recent years, there has been an effort by the Ethiopian Federal Ministry of Health to expand the service to other teaching hospitals as the unmet need is so huge. Updated information on factors predicting long-term survival rates can guide decisions, as can support from the Ministry. Even though the trend of breast cancer is increasing in Ethiopia [13, 22-24], there is a shortage of evidence on breast cancer in order to provide evidence-based intervention.

The result of this study will help identify possible risk factors that can be used by policymakers to raise community awareness and reduce morbidity and mortality. Identifying major determining factors of patient outcome and adherence helps advocate for the importance of adherence to improve patient outcomes and their quality of life. This study is also important to promote interventions like early diagnosis and early treatment of breast cancer, appropriate counseling, and prevention and control strategies, including national breast cancer screening.

Moreover, this study will provide caregivers with the necessary information regarding breast cancer in order to adopt a modified lifestyle, reduce the stigma attached to incurable diseases, and promote adherence to treatment. Finally, the study will serve as reference material for further research in related areas.

2. Literature review

In this section, different pieces of literature are reviewed. This literature review is collected from different sources, including journals, guidelines, PhD dissertations, and other published and unpublished materials. As much as possible, it is tried to find reliable, accurate, and up-to-date materials related to the study topic. In addition, the search was wide enough to identify all the relevant, appropriate, and useful literature. The search strategy was to use search engines and different key terms. Key terms were carefully chosen based on specific study objectives or research questions. A list of search terms was generated by combining terms related to the magnitude, risk factors, adherence, and outcome of breast cancer. In general, the review is organized as follows:

2.1. The biology of breast cancer

The term "cancer" refers to a group of diseases that result in the body's cells growing uncontrollably and in ways that are abnormal. Most cancerous cell types eventually develop a lump or mass called a tumor, which is named after the body region from which it originated. Breast cells give rise to the malignant tumor known as breast cancer. A malignant tumor is a group of cancer cells that can grow into nearby tissues or spread to distant parts of the body. Even though breast cancer happens mostly in women, men can also get it [1].

Breast cancer can be invasive or non-invasive. Invasive breast cancer is cancer that spreads into surrounding tissues and/or distant organs. On the other hand, non-invasive breast cancer does not go beyond the milk ducts or lobules in the breast. Breast cancers expressing estrogen receptors (ER) and/or progesterone receptors (PR) are "hormone receptor positive." About 10% to 20% of breast cancers depend on the gene called human epidermal growth factor receptor 2 (HER2) to grow. Those cancers are called "HER2-positive." HER2-positive breast cancers grow more quickly. Cancers that have no or low levels of the HER2 protein or few copies of the HER2 gene are called "HER2 negative. On the other hand, if a tumor does not express ER, PR, and HER2, it is called "triple negative." Triple-negative breast cancer makes up about 10% to 20% of invasive breast cancers. Triple-negative breast cancer seems to be more common among younger women [30]. In addition, breast cancer can also be divided into molecular subtypes as Luminal A, Luminal B, HER2-enriched, and basal-like based on mRNA gene expression levels [31].

2.2. Epidemiology of breast cancer

2.2.1. Magnitude and trend of breast cancer

Globally, cancer is a significant cause of morbidity and mortality, regardless of the level of human development. Based on estimates for 2020, there will be 19.3 million new cancer cases and 10 million cancer deaths. Breast cancer has exceeded lung cancer as the most commonly diagnosed cancer [32].

According to the Global Burden of Disease (GBD), among the 21 GBD regions, East Asia had the highest breast cancer incidence cases in 2019. In general, incident cases of breast cancer increased in all GBD regions, with the most significant trends observed in North Africa and the Middle East. Only North America and Australia showed a declining trend in age-standardized incident rates (ASIR) during the past three decades. East Asia was observed to have the largest increase in the ASIR. In 2019, countries with the highest incidence of cases included China, the United States of America, and India. In contrast, the largest decrease during this period was found in Greenland [33].

According to a study based on data from the Global Cancer Project in 185 nations, Belgium and Luxembourg had the highest rates of breast cancer worldwide (11.23 per 1,000 people and 109.3 per 1,000 people, respectively). On the other hand, Fiji (36.9 per thousand) and Barbados (33.1 per thousand) had the highest mortality rates [32].

Currently, the trends and status of breast cancer incidence and survival in European Union countries show that breast cancer incidence for women aged 25 to 39 years has been significantly increasing since the 1930s. This study also showed `that breast cancer incidence has been significantly increasing for the past 80 years [34]. High-income nations like the United States have a high incidence of breast cancer. Even though incidence rates are low, the mortality rate is higher in developing nations than it is in developed ones. In low- to middle-income countries, there were insufficient resources for various prevention and control measures, such as screening, early diagnosis, and treatment, which led to a higher mortality rate. The variations in incidence between nations can be attributed to the various population groups' changing environmental, behavioral, and lifestyle factors [34].

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A study done to examine breast cancer incidence and age-standardized rates showed that the incidence of breast cancer for women aged 25 to 39 years increased by 0.65% (95% CI, 0.53% - 0.77%) per year, from 16.3 breast cancer diagnoses per 100 000 women in 1935 to 38.5 breast cancer diagnoses per 100 000 women in 2015 [36]. In the period of 1980 to 2019, in the Northeast of Brazil, 65,531 deaths due to breast cancer were recorded in women aged 20 years and over. In all of the locations under study, a significant percentage increase in breast cancer mortality rates was observed when comparing the first five-year period (1980–1984) to the last five-year period (2015–2019). This increase was over 60%, varying from 62.0% in Alagoas to 222.00% in Maranh [37]. Based on another study done in Saudi Arabia, the incidence of breast cancer increased almost threefold, from 783 cases in 2004 to 2,240 cases in 2016. An increasing proportion of cases were diagnosed after age 45 (43%), increasing the median age at diagnosis [38].

The highest incidence rates of breast cancer have been found in the sub-Saharan African sub-region, with Africa currently having the highest age-standardized mortality rate worldwide. Concerns about incidence trends also exist, such as those surrounding naturally aggressive tumors and patients with breast cancer who are younger in age [8]. The population-based registries used in a systematic review of 22 African countries revealed that the overall pooled crude incidence of breast cancer was 24.5 per 100 000 person-years. In comparison to Sub-Saharan Africa (SSA), where the incidence was 22.4 per 100,000, North Africa had a higher incidence of 29.3 per 100,000. [39]. Similarly, according to a different study in SSA, BC is rising quickly in many regions of Africa; however, the size of those changes varies [40]. The annual number of women receiving a breast cancer diagnosis in sub-Saharan Africa is anticipated to nearly double by 2040, according to another report [12].

Magnitude of breast cancer in Ethiopia

The trend of non-communicable disease burden is increasing in the health facilities in Ethiopia. [21]. According to study data from Addis Ababa Mortality Surveillance data, based on the burial-based surveillance, there were 133,170 adult deaths from 2007 to 2017. The result showed that, cancer accounted for 11% of all deaths studied. Breast cancer was one of the most common causes of cancer death [41].

The study was done at Saint Paul Hospital Millennium Medical College, Ethiopia, from 2014–2018 [42]. Among a total of 2,002 female cancer patients who visited the Oncology Unit, cervical (46.7%) was the most frequent cancer, followed by breast (29.3%), and the majority of breast cancer cases were observed among younger patients [42]. Based on another retrospective study done among breast cancer patients diagnosed between 2013 and 2019 at Hawasa University, 559 (18.6%) breast cancer cases Of those, 548 (98%) were women. The majority of patents, 372 (66.5%), had advanced breast cancer (Stages III and IV). Additionally, the disease was developing at a young age, based on the age at diagnosis. In addition, breast cancer also showed an upward trend [43].

Another retrospective study done at Tikur Anbessa Specialized Hospital over a period of sixteen years also found that there were 3460 new cases of breast cancer registered at the cancer registry during the 16-year period [23]. A similar study done in Jimma University Specialized Hospital on patients who underwent fine needle aspiration cytology for breast complaints found that, from a total of 683 cases, 598 (89%) and 75 (11%) were females and males, respectively. In general, there was an increasing trend of breast cancer in the study area over subsequent years. The highest prevalence of breast cancer was noted in women who were in their sixth and seventh decades of life. In addition, patients with breast cancer wait a significant amount of time before looking for health care, and more than half of the cases come with locally advanced cancer [44].

2.2.2. Risk factors for breast cancer

Breast cancer is caused by a complex interplay of multiple factors including age, genetics, environment, and reproductive history and probably yet unknown factors. Breast cancer is more prevalent in post menoposal women and its risk rises wise age. The development of breast cancer

is significantly influenced by genetic and hereditary factors. The risk of breast cancer is markedly increased by first-degree family history. Obesity, alcohol use, smoking, physical inactivity, and replacement hormone therapy are all potentially modifiable factors that have been linked to an increased risk of breast cancer. Risk is also influenced by a woman's reproductive history, with null parity being associated with higher rates than multiparty. Understanding its pathophysiology and etiology both help to focus on crucial preventative steps that can be performed to lower risk. Understanding the etiology causes of breast cancer helps improve screening methods, therapies, and patient counseling and education. [45].

Breast cancer is linked to a number of well-known factors. Most of these factors cannot be altered well-known factors. Most of these factors cannot be altered. Sex (being a woman), age, family history, early menarche, and late menopause are risk factors that cannot be changed. Contrarily, modifiable factors include breastfeeding, postmenopausal obesity, and the use of menopausal hormones that combine estrogen and progestin. The duration of breast tissue's exposure to hormones is influenced by a number of breast cancer risk factors. Regular physical activity, preventing weight gain and obesity, and consuming less alcohol are all interventions that may help lower the risk of breast cancer [1]. Breast cancer incidence and mortality rates have increased with altered risk factor profiles, enhanced cancer registration, and improved case detection. There are a significant number of risk factors for BC, both modifiable and non-modifiable [31].

Biological and physiological factors

About 5% to 10% of breast cancer cases are assumed to be hereditary or directly related to gene changes (mutations) passed on from a parent [42]. The most common cause of hereditary breast cancer is an inherited mutation in the BRCA1 or BRCA2 genes. In normal cells, these genes help make proteins that repair damaged Deoxyribonucleic acid (DNA). Mutated versions of those genes can lead to abnormal cell growth, which can lead to cancer. On average, a woman with a BRCA1 or BRCA2 gene mutation has up to a 7 in 10 chance of getting breast cancer by age 80 [46].

Socio-demographic factors associated with breast cancer

Socio-demographic factors include age, education, marital status, place of residence, and occupation. A study done in India among a total of 1210 cases found that 46% of patients reported early stages and 54% advanced stages. Patients of rural residence and of low educational status are more likely than their respective counterparts to have an advanced stage of BC diagnosis [47]. Another study from India discovered that patients with lower educational status those with only a primary school education were significantly more likely to have breast cancer that was already in an advanced stage than patients with higher educational status [48]. Another study from Mexico also found a significant association between breast cancer screening practices and educational status [49].

According to a study conducted on the demographic and clinical profiles of patients diagnosed with breast cancer in Iraq, the mean age at presentation was 51 $\pm$10.6years; patients under the age of 50 constituted 46.8%, 42.2% were 50–64 years, and 11% > 65 years. In general, 88% were married, 22.4% were illiterate, whereas 30.3% were primary, 23.1% were secondary, and 19.2% graduated from universities [50]. Another study conducted in the Gaza Strip also showed that there was a significant association between breast cancer and educational status and marital status [51].

Another study done among 100 patients and 200 healthy controls in Babylon Province showed that low economic status was significantly associated with breast cancer. However, levels of education did not show a significant association with breast cancer [52]. On the other hand, a study from Mozambique showed that a higher educational level increased breast cancer risk [53], while a study from Northern Algeria showed that a low education level was associated with higher BC risks [54]. A similar case-control study done in the Central African Republic showed that women with breast cancer were more likely to have little or no education and be married [55]. Similarly, according to a study done in TASH, the highest age of incidence was the 4th and 5th decade, and most of the cases were found in Addis Ababa, where the hospital is located [23].

Reproductive risk factors

The risk of breast cancer increases among women who have first-degree relatives with breast cancer. However, the majority of women diagnosed with the disease do not have a known family history of the disease. A lack of a known family history does not necessarily mean that a woman is at reduced risk [10]. A case-control study done to assess the determinants of breast cancer among 100 cases and 100 control women in terms of reproductive factors showed that age at menarche, age at first birth, parity, and history of breast feeding are risk factors for breast cancer in women [56]. However, menopausal age was not a risk factor for breast cancer in women.

According to a study done in Iran on 39 studies, factors including a family history of breast cancer and abortion play a significant role in the occurrence of breast cancer [57]. On the other hand, late menarche, null parity, and long breast feeding duration showed a significant inverse relationship with breast cancer occurrence [57]. In addition, another study done in Babylon Province among 100 cases and 200 healthy controls found that the late age of menopause and positive family history were significantly related to breast cancer. The age of menarche did not show a significant association with breast cancer [52]. Another study done among 138 cases and 638 controls in Mozambique from 2014 to 2017 showed that multiparty was considered a preventive factor for the development of hormone receptor positive and negative tumors [53].

Another study done among women with breast cancer in Kenya showed that there was no significant difference in breast cancer tumor characteristics or molecular subtypes; however, there were significant differences in reproductive factors and socio-demographic characteristics between the three main ethnic groups [58].

Behavioral and environmental risk factors

A study found that heavy smoking over a long period of time might be associated with a somewhat higher risk of breast cancer. The risk has been highest in certain groups, such as women who started smoking before they had their first child [46]. A study from 23 centers in 10 European countries showed that there was a positive association between breast cancer and alcohol consumption and suggested an inverse association between dietary fiber and possibly fruit intake and breast cancer risk [59]. Another study done in the UK also found that greater

physical exercise is related to a reduction in breast cancer risk, which seems to be independent of any association it may have with risk through its effects on adiposity [60]. A study done in Korea also found that milk consumption in Korean women less than 50 years of age is associated with a decreased risk of breast cancer compared to those who never or rarely consume milk [61]. Another study from Iran also showed that being a passive smoker and consuming sweets play a significant role in the development of breast cancer. On the other hand, regular physical activity and consumption of vegetables showed a significant inverse association with breast cancer [57].

According to another case-control study done in the Gaza Strip, the key statistically significant risk factors of breast cancer were: physical trauma on the breast; medication for infertility treatment; eating canned food; eating red meat (500g or more weekly); eating raw and cooked vegetables; eating chicken skin; using oils with saturated fats in cooking; living in or beside a farm; cleaning pesticides' equipment; living with people working in a farm or an agricultural field; working in a farm during pesticide application or during 24 hours of pesticide application; and applying pesticides personally [51].

Another study from Babylon Province showed that use of contraceptives was significantly related to breast cancer, whereas exposure to cigarette smoking did not show a significant association [52]. A study from Mozambique also showed that higher weight and BMI were linked with a higher breast cancer risk among postmenopausal women [53].

2.3. Profile of breast cancer Patients

2.3.1. Hematological profile and breast cancer

Significant variances were detected in the values for RBCs, WBCs, platelet count, PCV, and lymphocytes among breast cancer patients, according to a study of variations in hematological and biochemical parameters carried out in Babylon province. In comparison to controls, patients' mean values for RBCs, WBCs, platelets, PCV, and lymphocytes were considerably lower [62]. Another study from Malaysia found that 22% of patients with breast cancer had hemoglobin values that were significantly below normal [63]. Hematological measures were identified as significant investigations and helpful prognostic factors in another Chinese study that examined the efficacy of risk stratification in patients with breast cancer [64].

Similarly, a study done in Mysuru, India, from January 2013 to June 2016 among 156 cancer cases and 102 controls also found that RBC, hemoglobin (Hb), and erythrocyte sedimentation Rate (ESR) were significantly low among breast cancer patients [65].

A study of variations in hematological and biochemical parameters conducted in Babylon province showed that significant differences were found in the values for RBCs, WBCs, platelet count, PCV, and lymphocytes among breast cancer patients. The mean RBCs, WBCs, platelets, PCV, and lymphocyte values were significantly lower among patients compared to the controls [62]. Another study from Malaysia also revealed that 22% of breast cancer patients had significantly decreased hemoglobin values [63].

Another study conducted in China also indicated hematological parameters as important investigations that are useful prognostic factors for evaluating the accuracy of risk stratification in breast cancer patients [64]. Similarly, a study done in Mysuru, India, from January 2013 to June 2016 among 156 cancer cases and 102 controls also found that RBC, hemoglobin (Hb), and erythrocyte Sedimentation Rate (ESR) were significantly low among breast cancer patients [65].

Another case-control study conducted among 70 cases and 20 controls in India also revealed that the red blood cell (RBC) count, lymphocyte count, and hemoglobin concentration were significantly lower among cases compared to controls [66]. A study from the University of Calabar Teaching Hospital, Nigeria, among 36 female breast cancer patients and 30 controls found that the mean values of hemoglobin concentration and packed cell volume were significantly lower ($p = 0.001$) among patients compared to values from controls. In addition, breast cancer patients had significantly lower values of the total white blood cell count as well as absolute neutrophil and lymphocyte counts compared to control subjects [67].

A study done in Algeria to evaluate the variation and importance of certain hematological parameters in women with breast cancer under chemotherapy treatment showed that parameters under the erythrocyte line (RBC, HGB, and HCT) were significantly decreased [68]. A similar study was done in the Oncology Unit of Ayder Comprehensive Specialized Hospital, Mekelle, and Northern Ethiopia, aiming to compare hematological parameter changes in pre- and post-chemotherapy among cancer patients. It showed that of the 376 study participants, 228 (60.6%)

were female [65]. All the hematological profiles, except lymphocyte count, showed significant decrements post-chemotherapy compared to pre-chemotherapy [69].

2.3.2. Blood group profile of breast cancer patients

ABO blood group was discovered in 1900 and 1901 at the University of Vienna by Karl Landsteiner in the process of trying to learn why blood transfusions sometimes cause death and at other times save a patient. In 1930, Karl Landsteiner belatedly received the Nobel Prize for his discovery of blood types. All humans and many other primates can be typed for the ABO blood group. There are four principal types of ABO blood group: A, B, AB, and O. There are two antigens and two antibodies that are mostly responsible for the ABO types. The specific combinations of those four components determine an individual's blood type in most cases [70].

Now days there are more than 30 different blood types, but ABO and Rhesus (Rh) blood group system are very important since those blood group antigens have very strong immunogenicity [70]. Within the ABO groups, it is likely for the red cells to have either of those antigens on their surface, or both, or neither. Cells that only have the A antigen are called group A. Those that only have the B antigen are named group B. Cells that have both the A and B antigen are named group AB, and cells that lack both A and B antigens are named O. The clinical importance of the Rh blood group system was clearly established by Levine and Stetson in 1939 when, following the delivery of a stillborn baby, a patient urgently required a blood transfusion [71].

The Rh blood group system is second only to ABO in clinical importance, since the Rh antigens, especially D antigen, are highly immunogenic and the antibodies can result in delayed hemolytic transfusion reaction (HTRs) and hemolytic disease of the fetus and newborn (HDFN) [72]. Rh system contains at least 45 antigens of which the main antigens are D, C, E, c, and e. The Rh system is a complex system, and controversy over its genetics has resulted in the development over time of multiple nomenclature systems. In 1943 Wiener proposed the idea of a single Rh locus with multiple alleles [73].

Persons with Rh negative (-) blood group represent a very small proportion, while in Europe, America, Australia, the Rh negativity rate is much higher, accounting for around 15% - 40% of the population. The role of ABO blood group in cancer biology has been studied by several investigators [75]. The ‘‘ABO” and ‘‘Rhesus” blood type system is the most significant basis in transfusion medicine; however, there appears to be susceptibility to some diseases including, risk of breast cancer associated with some blood genotypes [76].

In 1953, the first association between the ABO blood group and cancer was established [77]. The genomic structure of ABO genes contains seven exons that span approximately 19 kilobases (kb) of genomic DNA on chromosome 9, band q34. Most of the coding sequence is located in exon 7. Analysis of the 5' upstream region revealed the presence of the binding site for transcription factors and enhancer elements. Studies have been done on the genetic underpinnings of blood group A and B phenotypes abnormally expressed in various types of human cancer. A or B epitope deletion, which is frequently seen in a wide range of human cancers and is accompanied by an accumulation of their precursor H (Le(y), Le(b)), leads to increased malignancy [78].

The genetic regions at 9 q34.2, where ABO blood group genes are located, are frequently altered in cancers. For many human malignancies, including colon, breast, and prostate cancer, the expression of blood group antigens in tumors has been linked to metastasis and prognosis because the blood group carbohydrates expressed on the cell surfaces of metastatic cancer cells serve as cell adhesion molecules [79].

In cancer patients, the occurrence of the A group was higher in breast, lung, bladder, and kidney cancers, though when all cancers were combined, the incidence of the B blood group was highest, followed by the A group. Numerous diseases have been linked to the ABO blood type, an easily accessible element of a patient's genetic makeup. The relationship between the ABO blood group and cancer susceptibility has been the subject of numerous other reports over the past 60 years, but the exact reason why this relationship exists between some diseases and the ABO blood group is still unknown. However, based on studies, tumor cell adhesion,

membrane signaling, and host immune response to ABO antigens emerge as a result of interactions between ABO alleles and inflammatory markers [78, 80]. Many studies have sought to determine whether the histoblood ABO group is associated with tumor genesis [81-83].

Women with blood type A had a high risk of breast cancer, whereas women with blood type AB had a low risk, according to numerous studies conducted in various nations [81-84]. However, a study from Kuffa, Iraq, discovered a link between blood group O and a higher risk of breast cancer [85]. On the other hand, a study done in India found that blood group B was the dominant blood type in breast cancer patients; however, it did not show a statistically significant association [86].

Similar to the ABO blood group system, the association between the Rh blood group and breast cancer is also inconsistent. Some, including the genome-wide association studies, have established a relationship between breast cancer and Rh type [85-87], whereas others did not show an association [87]. The ABO blood group may affect the risk of different diseases by different types of mechanisms, which can be known or unknown [88].

The proportion of the population belonging to each blood group differs with race type [89]. Besides the controversies and uncertainties' concerning the relationship between ABO/Rh and breast cancer, the most likely mechanism in the progression of an association between blood types and the incidence of breast cancer has not been established yet. Thus, more evidence from different population groups is needed, and this study will add to the body of literature for future studies by assessing the frequency and association of the ABO blood group with breast cancer in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

2.4. Breast cancer Management and Prevention

2.4.1. Diagnosis of breast cancer

Early diagnosis and treatment are essential to reducing breast cancer-related deaths. The ways in which cancer is diagnosed and treated have changed dramatically over the past 20 years. Additionally, these techniques focused on managing and treating the disease with little discomfort for the patient, greater patient compliance, and fewer side effects [90].

There is low priority given to cancer in health care services in Sub-Saharan Africa. A study showed that there are several inequalities in cancer diagnosis and screening between different African regions that can be one of the main reasons for variations in cancer incidence and mortality rates across regions. There are pending concerns regarding cancer care on the continent. The result also found that the African countries suffer from a lack of adequate medical equipment, supplies, and human power, including epidemiological expertise and research resources [91].

A study conducted in four sub-Saharan African nations Kenya, Burkina Faso, Ivory Coast, and Namibia found that only 12.9% of women underwent breast cancer screenings overall during the study period. In Ivory Coast, this percentage was the lowest (5.2%), while in Namibia, it was 23.1%. In sub-Saharan Africa, breast cancer screening rates are notably low and vary widely between nations, despite higher breast cancer mortality rates. Age, education, health insurance coverage, and the level of the household wealth index all play a role in this difference. Countries with the highest prevalence of breast cancer screening were Namibia, followed by Kenya, Burkina Faso, and Ivory Coast [92].

2.4.2 Treatment of Breast Cancer

Breast cancer treatment is multifaceted and involves a variety of techniques such as surgery, chemotherapy, hormonal therapy, radiotherapy, or biological therapies that are administered in different order. [10, 31]. Breast cancer treatment can be highly effective, achieving survival probabilities of 90% or higher, particularly when the disease is identified early. In the past, all breast cancers were treated surgically by mastectomy (complete removal of the breast). When cancers are large, a mastectomy may still be required. Today, the majority of breast cancers can be treated with a smaller procedure known as a "lumpectomy" or partial mastectomy, in which only the tumor is removed from the breast. In these cases, radiation therapy to the breast is generally required to minimize the chances of recurrence [10].

According to review conducted in USA, mortality rate is reduced by early detection and treatment of breast cancer [90]. On the other hand, in most sub-Saharan African countries oncology care facilities are few and are overstretched. As a result, treatment can be lacking and/or waiting times for chemotherapy and radiotherapy (if available) are long [12].

Despite the fact that breast cancer is the most common cancer in SSA, little is known about the actual treatments that patients receive and their survival rates among the general population [93]. In 10 nations, including Cote d'Ivoire, Benin, Congo, Kenya, Mali, Mozambique, Uganda, Ethiopia, and Zimbabwe, urban population-based cancer registries show that 809 patients received cancer diagnoses between 2009 and 2015. Additionally, 517 patients (63.8%) had additional data gathered on them. The study also revealed that only one out of every five traced patients met the minimal diagnostic standards. For 72.5% of patients, the status of the hormone receptor was unknown. Only half (50.9%) of the stage I–III BC patients who were tracked received insufficient or no cancer-directed therapy [93].

Women with breast cancer in SSA are younger than those in high-income countries, according to a study conducted there. The majority of women with advanced disease stages have poor prognoses due to the lack of effective treatments. There is frequently a delay between the first disease symptom and seeking medical attention. Furthermore, low participation in early detection methods like mammography and breast exams makes a diagnosis more difficult to make earlier on. Due to financial, logistical, and sociocultural limitations, the majority of SSA countries have not been able to implement and maintain screening programs. Mammography has many limitations in SSA and is likely to have a higher harm-to-benefit ratio than it does in high-income countries, where it is widely used. The combination of a late stage at diagnosis and limited treatment facilities severely limits a woman’s hope of full recovery from breast cancer [94].

According to a study conducted in various healthcare facilities throughout Africa, including Nigeria, Uganda, and Namibia, 227 (17%) of the total 1325 women with cancer had not begun treatment within a year of their diagnoses [95]. In two regional hospitals in Nigeria, the percentage of untreated patients was highest (38% of 314 women, 32% of whom were in stages of the total 1325 women with cancer had not begun treatment within a year of their diagnoses

[95]. In two regional hospitals in Nigeria, the percentage of untreated patients was highest (38% of 314 women, 32% of whom were in stages I–III). 18% of 430 women at a national referral hospital in Uganda received no care, with stage I–III patients making up 15% of those [95]. In contrast, all non-black women (100%) and 98.7% of black women had started treatment at a cancer treatment facility in Windhoek, Namibia, where care is offered at no cost to the patient. Women from lower socioeconomic groups and women who believed in conventional medicine had higher rates of untreated pregnancies.

A study conducted in Nigeria found that of a total of 82 patients, 81 (98.8%) were female, and the majority (65.4%) were premenopausal. All patients had breast lumps with a mean duration of 9.49±6.1 months and a size of 2–16 cm (mean 7.9±3.4 cm). Ten (12.2%) patients had early onset, 61 (74.4%) had locally advanced disease, and 11 (13.4%) had distant metastases. Fifty-one (62.2%) patients underwent mastectomy. Only 38 patients (46.3%) completed six courses of chemotherapy. No immunohistochemistry was performed on any of the patients, but all were taking tamoxifen regularly. Only four of her patients (4.9%) received radiotherapy. Nineteen (23.2%) died within one year of onset [96].

A study conducted at the University of Gondar Hospital Cancer Center, Ethiopia, revealed that among 82 treated patients, late diagnosis and an advanced stage of disease at the time of diagnosis were seen in most of the patients. Chemotherapy was administered to 79 (96%) patients [97].

Another study done among a total of 128 breast cancer patients treated at Felege Hiwot Referral Hospital, Bahir Dar, Ethiopia, found that the majority, 119 (93%) of the patients, were female. Most of the patients, 67 (52.34%), had advanced stage IV cancer that reduced their chance of recovering after treatment. Moreover, patients who received chemotherapy and surgery for breast cancer were more likely to improve than patients who received only chemotherapy. As the stage of breast cancer advances, the chance of the patient's status improving decreases. Patients from rural areas, where healthcare services are rarely available, were less likely to recover or improve compared to those from urban areas [98].

2. 4.3. Adherence and associated factors towards breast cancer treatment

Adherence can be defined as the extent to which patients follow the instructions they are given for prescribed treatments. This definition was somewhat extended by the WHO as ‘the extent to which a person’s behavior of taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a health care provider" [99].

A study conducted in Jordan found that of a total of 553 patients, 114 (20.6%) had metastatic disease at presentation. Patients were treated less aggressively. 144 patients (32.8%) with primary disease and 98 (86.0%) with metastatic disease did not receive chemotherapy [100]. Another study conducted to evaluate adherence to endocrine therapy and aromatase inhibitors in patients with BC at the Khartoum Oncology Hospital in Sudan found that of a total of 172 patients, the majority (45.9%) had stage III disease. It was shown that there was additionally, almost half (49.4%) were postmenopausal women. The majority, 93% of the study group, had greater than 80% adhesion to tamoxifen (TAM) and aromatase inhibitors (AIs). Furthermore, a statistically significant association was found between adherence to hormone therapy (>80%) and the poor or average financial status of patients and married women [101].

A study conducted at Aira Hospital in rural Ethiopia showed that of the 26 patients (51%) who were started on tamoxifen, only 9 (35%) remained on treatment. Medication possession rate: ≥80%, median follow-up: 16.2 months. Of 26 patients (51%) who were started on tamoxifen, only 9 (35%) remained on treatment. Medication possession rate: 80%; median follow-up: 16.2 months. After 1 year, 52% of patients were still on treatment, and 9 patients discontinued treatment. Reasons for not starting tamoxifen treatment include patient factors such as financial difficulties and a lack of transportation [102].

A study conducted on breast cancer patients at the Tikur Anbessa Specialty Hospital in Addis Ababa, Ethiopia, found an overall adherence to AHT compliance rate of 77.5%. Factors such as type of adjuvant hormone therapy, presence or absence of side effects, mastectomy, use of social support, and thorough treatment communication were closely associated with treatment adherence [103].

2.4.4. Treatment outcome of patients treated for breast cancer

Survival is extremely determined by stage of the disease and tumor size; for example, 5-year relative survival is 99% for localized disease, 85% for regional disease, and 26% for distant-stage disease [1, 31]. Regarding tumor size, among women with regional disease, the 5-year relative survival is 95% for tumors less than or equal to 2.0 cm, 84% for tumors 2.1–5.0 cm, and 70% for tumors greater than 5.0 cm [1,31]. Survival rates for all European Union (EU) countries show a significant increase, but most former Eastern Bloc European countries still record lower survival rates compared to other countries within the EU. The overall survival improvement shown across all EU-28 countries will probably be amplified as more of the Eastern Bloc countries reach a higher economic status and beneficial treatments become available to all European citizens [104].

Based on the study, high survival rates of breast cancer were observed in the Northern and Western European countries, with the exception of the Baltic countries. In general, higher survival rates are attributed to early diagnosis and treatment, better access to beneficial treatments, and improved general health care services [34].

A cancer registry database from East Azerbaijan and Iran for the 10-year period between 2007 and 2016 found that one-, two-, three-, five-, and ten-year breast cancer-specific survival proportions were 0.92, 0.88, 0.84, 0.77, and 0.65, respectively. Older individuals had significantly worse survival, and patients with high-grade tumors had a significantly higher risk of mortality [105].

According to a study from Jordan, overall 5-year survival was 67.6%. [100]. Survival was significantly improved for patients with non-metastatic disease (78.8% vs. 25.4 %) and for those with node-negative compared to node-positive disease (85.4% vs. 74.1%). Based on the result of the Cox regression analysis, only positive lymph nodes were associated with a poor outcome [96]. Another study done to assess the survival of patients in China showed that the 3-year BCSS rates were 63.24% for ipsilateral supraclavicular lymph node metastases (ISLM), 64.54%, and 41.20% for distant lymph node metastases (DLNM) [106]. Loco regional treatment was associated with significantly improved survival for patients with DLNM [106].

A study done on breast cancer patients in Indonesia found that the most significant factors for survival were the chemotherapy regimen, hormonal therapy, and stage of the disease. The stage of cancer had a significant impact on decreasing patient survival. The higher the stage, the more difficult it was to treat and the shorter the patient's life expectancy. Chemotherapy treatment with the right regimen and hormonal therapy as a follow-up treatment also dramatically determined the patient's survival [107]. Another Brazilian study of 1113 breast cancer patients found that the mean age at diagnosis was 52 years (SD 13.5). Unlike most developing countries, the majority of patients were diagnosed at an early stage, which is stage 0 and I (62.7%), while only 1.3% had stage IV disease. Five-year and 10-year overall survival rates were 93.5% and 83.8%, respectively. According to multivariate analysis, age at diagnosis, stage III or IV, and distant relapse were significantly associated with survival. Breast cancer mortality appears to be dependent on the quality of health care provided to patients [108].

Another hospital-based retrospective cohort study conducted in a specialized cancer center in Brazil found that most stages were classified as I and II (60%). Overall survival was 82.7% in 2000–2004 and 89.9% in 2010–2012 ($P < 0.001$). In patients with invasive ductal cancer who received surgery and hormone therapy, the risk of death decreased in the recent period. In general, early diagnosis and combination therapy are predictive prognostic factors for high survival in patients with invasive breast cancer [109].

A study conducted through the African Cancer Registry Network showed that patients diagnosed at an early stage had a 3-year RS of 78%, compared to 40.3% of advanced (III and IV) women [110]. Another study involving 11 urban population-based cancer registries from 10 SSA countries found 50.9% of patients with stage I-III BC (n = 320) received inadequate or no anticancer therapy. Initiation of appropriate treatment and early diagnosis were the most important factors influencing survival [93].

A systematic review conducted in Africa showed that breast cancer patients had poor survival as the incidence of the disease increased. The result also showed that five-year survival rates adjusted for gender and age were lower in sub-Saharan Africa than in North Africa. African survival rates remained significantly lower compared to blacks (76% in 2015) and whites (90%). in 2015) population in the United States [111].

A study conducted at TASH, Addis Ababa, from 1995–99 showed that the majority of cases (60.2%) were at stages III and IV. Invasive ductal carcinoma was the most frequent type (77.6%). Eighty-nine (71.2%) patients underwent a modified radical mastectomy and 103 axillary dissections. During a short follow-up, 50 (45.9%) of 109 patients were seen with recurrences. Two people (4%) died from the disease. The condition of 15 (12%) was unknown; 11 had stage IIIB or IV. Short-term clinical disease-free or improved survival was observed in cases of stage II disease regardless of age and in those that received multimodality therapy. Only four cases were seen at 5 or more years [112].

Another cohort study conducted on 1,070 women to see breast cancer survival at TASH, Ethiopia, showed that nearly all patients (87%) underwent surgery [113]. The majority had a modified radical mastectomy (95%). Of all chemotherapy patients, 753 (83.7%) received a full six cycles of chemotherapy. About 79% of patients with chemotherapy started treatment within 6 months, and 77% of patients with endocrine therapy started treatment within 12 months after surgery. In 285 women (26.6%), distant metastasis occurred during follow-up. At the end of the study, 78% of women had completed follow-up. Metastasis-free survival (MFS) of patients after 2 and 5 years was 74 and 46%, respectively. The 5-year MFS was 72% for stages 1 and 2 and 33% for stage 3. Women aged 60 years and above also tended to have a worse prognosis compared with those aged 50–59 years [113].

2.5. Prevention of breast cancer

Because breast cancer development is a multistep process involving multiple cell types, its prevention remains a challenge worldwide. In recent decades, many advances have been made in understanding breast cancer and developing preventive methods. Although the incidence is high in developed countries, almost half of breast cancer cases and more than half of all deaths occur in developing countries. It is a preventable disease, and developed countries have adequate medical resources to protect against it [114].

Evidence is convincingly mounting for the benefit of incorporating exercise into breast cancer prevention and treatment. Despite the many benefits of exercise in the prevention and control of breast cancer, an inability to successfully engage patients and health care professionals will drastically limit any impact on public health [115]. Multicomponent interventions to increase

breast cancer screenings have the greatest effect on community health. Multicomponent interventions include increasing community demand, access, and screening procedures and delivery in communities [116]. A review in the United States concluded that current strategies to reduce a woman's risk of developing the disease are primary prevention strategies, such as avoiding tobacco, using external hormones, excessive exposure to ionizing radiation, and maintaining a normal weight [117].

In another review in Latin America, 20 (2.7%) of the 743 included studies were selected and analyzed using descriptive statistics and qualitative content analysis [94]. The selected studies identified several Latin American countries that have developed policies and programs for the prevention and control of breast cancer in women. These programs focus mainly on risk communication, prevention, timely detection, effective access to health services, improvement of the examination process and screening. There is still a lack of evaluation criteria and greater participation of civil society in political planning and program implementation [118].

2.6. A brief description of conceptual framework

Cancer in general and breast cancer in particular are major public health problems in developed and developing countries. This is mainly due to an increase in the number of women, an aging population, fewer and later pregnancies, earlier menarche, later menopause, shorter breastfeeding, increased alcohol consumption, obesity, and inactivity.

Breast cancer has different risk factors. Some of those factors cannot be changed or are not modifiable, such as sex, age, race, genetic factors, reproductive history, and family history. On the other hand, there are factors that are modifiable or can be changed; those include education or awareness, short or no breast feeding, alcohol consumption, obesity, hormone replacement therapy, birth control pills, and inactivity [9, 10]. All those factors are directly or indirectly linked to the level of adherence and outcome of breast cancer patients.

Level of adherence can be affected by many factors, including health-related factors (like accessibility and treatment cost), patient-related factors (like socioeconomic status and educational status), therapy-related factors (such as drug side effects), and social-related factors (such as cultural factors). Non-adherence can contribute significantly to the variability of treatment effectiveness and determine the outcome of patients [18, 19]. Survival is extremely determined by many factors, including the stage of the disease, tumor size, and the duration between the first symptom and treatment. According to global cancer statistics, the survival rate is the lowest for late-stage breast cancer; however, earlier detection and improved treatment have resulted in a rise in survival rates. There is also a clear decrease in survival with increasing age at diagnosis. There is a significant relationship between survival and treatment adherence; patients with good adherence have better survival compared to patients with poor adherence (Figure 1).

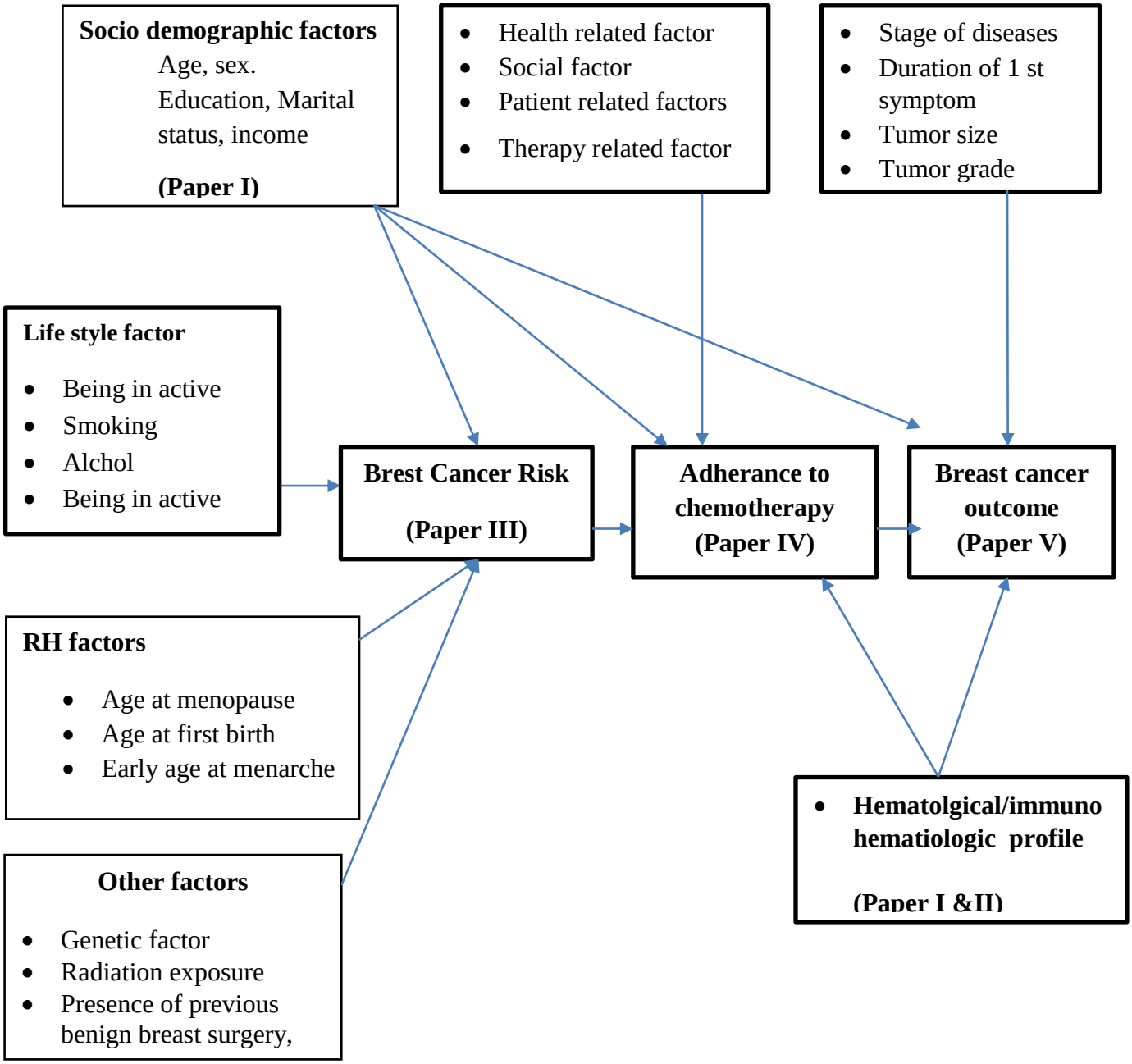


Fig. 1 Conceptual framework that shows breast cancer risk, adherence and outcome summarized from different litratures

3. Objectives of the study

3.1. General objective

To assess the epidemiology of breast cancer among patients treated at the Oncology Department, Tikur Anbessa Specialized Hospital, and Addis Ababa, Ethiopia.

3.2. Specific objective

- To describe the socio –demographic and hematologic profile of patients with breast cancer at Tikur Anbessa Specialized and Teaching Hospital. (Paper I and II).
- To identify risk factors for breast cancer patients (Paper III).
- To determine chemotherapy treatment adherence and associated factors among breast cancer patients treated at Tikur Anbessa Specialized and Teaching Hospital (Paper IV).
- To determine survival of breast cancer patients treated at Tikur Anbessa Specialized and Teaching Hospital. (Paper V)

4. Materials and Methods

4.1. Study area

This study was conducted in Addis Ababa at Tikur Anbessa Specialized Hospital (TASH), Oncology Department. The Oncology Center of TASH was the only institution that provided radiotherapy services in Ethiopia at the time of the study. With the support of Ethiopia's governmental institutions, NGOs, and international partners, the hospital is hoping to develop a comprehensive program, including a cancer registry, early detection, prevention, standard treatment, and palliative care. At the time of the study, the hospital had one CT scanner and one MRI scanner. The hospital had 700 beds, of which 18 were allocated for cancer treatment. Of the 201 physicians in the hospital only two were hematologists, four were oncologists, four were radiotherapists, two were surgical oncologists and one was a pediatric oncologist. Three palliative pain specialists also worked at the Hospital. Only 26 of the TASH's 627 nurses were dedicated oncology nurses [119]. The study was conducted from May 2018 to January 2021.

4.2. Study design

In this study, multiple epidemiological study designs, including case control, cross-sectional, and retrospective cohort study designs, were applied. A hospital-based case-control study was done in order to assess the sociodemographic and hematologic profiles of breast cancer patients (objective 1) and identify risk factors for breast cancer **(objective 2).** Moreover, a cross-sectional study design was used to assess the treatment adherence of breast cancer patients treated with chemotherapy (objective 3). In addition, a retrospective cohort study was also used to determine the survival of breast cancer patients **(objective 4).**

4.3. Source and Study Population

For the case-control study **(Objectives 1 and 2),** breast cancer patients referred to TASH's Oncology Department were used as the source population. On the other hand, all females free from breast cancer who were caregivers for cancer patients at the Oncology Department were the source population for controls. Newly diagnosed female breast cancer patients referred to TASH, Oncology Department who fulfilled inclusion criteria and gave informed consent were the study participants. On the other hand, 18-year-old and older female caregivers free from breast cancer that fulfilled the inclusion criteria and were willing to participate were the study participants as controls. Regarding the cross-sectional study, for measurement of adherence **(Objective 3**), all newly diagnosed female breast cancer patients participating in the case-control study were used as the source population, and patients who had fulfilled the inclusion criteria were used as the study population. Concerning the study outcome or survival analysis **(Objective 4),** all breast cancer patients treated from September 2010 to August 2014 were used as the source population. Patients with complete records that fulfilled the inclusion criteria were used as the study population.

Eligibility criteria for a case-control study

Inclusion criteria

Inclusion criteria for breast cancer cases

For the case-control study **(objectives 1 and 2),** all newly diagnosed breast cancer patients with confirmed histology results who were well informed, well enough to communicate during the interview process and selected by the sampling procedure of the study were included in the study. In addition, patients with no observable psychiatric or mental disorders, no history of another cancer, or other chronic diseases such as hypertension or diabetes were also included. For the cross-sectional study or measurement of adherence (objective 3), all breast cancer cases used for the case-control study were included.

Regarding the retrospective study (Objective 4), records of breast cancer patients diagnosed from September 2010 to August 2014 were used to assess the survival of breast cancer patients. Patients with complete records and at least two follow-up visits were included in this study.

Inclusion criteria for controls

For objectives 1 and 2, newly diagnosed breast cancer patients aged 18 years and older were included. Regarding controls, women caregivers free from breast mass after physical examination, well enough to communicate, and selected by the sampling procedure of the study were included in the study.

Exclusion criteria

- For the case-control study **(objectives 1 and 2),** healthy controls and caregivers with chronic diseases, pregnant women, and women who have biological relationships with selected cases were excluded from the control group.
- For the measurement of adherence **(objective 3),** since it was difficult to get adequate information to assess their adherence status, patients referred to regional chemotherapy centers, patients moved to private health facilities, patients who died before and after imitation of chemotherapy, and patients whose phones were not working were excluded from the analysis.
- For survival analysis **(objective 4),** those patients without phone numbers in their file were excluded. During the follow-up period, women with unknown outcomes (patents with death or being alive) were excluded from the analysis.
- For all objectives (1-4), male breast cancer patients were excluded.

4.4. Sample Size and sampling method

Tikur Anbessa Specialized Hospital (TASH) was selected for the study since it was the only referral center for cancer treatment during the study period. Concerning the selection of the study participants histologically confirmed and clinically staged cases of breast cancer patients and respective controls were selected. During the selection of cases, breast cancer cases were proven by histopathology, and they were not suffering from any major chronic illness in the past, before the diagnosis of breast cancer. On the other hand, controls were women caregivers free from breast cancer based on physical breast examination. For the assessment of survival measurement, all eligible patients were included based on the inclusion criteria.

For the case control study, sample size was determined based on a double proportion formula using an online sample size calculator by assuming: Z_{β}=.80% power, Z_{α} = 0.05 significance level at 95% CI, r=1 Equal number of cases and controls, P1=Breast cancer exposure in control group, which was 11.9%, age $\geq$ 60 years is considered as a risk factor for breast cancer [120]. P2= breast cancer exposure among cases, which is 21.6%. Finally, the total sample size was 466(233 cases and 233 controls) and OR of 2:00 to be detected as significant association.

For the cross sectional study to determine breast cancer chemotherapy adherence (objective 3), all breast cancer cases were planned to be included in the study, but some of the patients were excluded due to different reasons, including death, having moved to private or other regional chemotherapy center, and having planned for other forms of therapy) For this reason, the remaining breast cancer cases that had chemotherapy were included in the study. In this case, a total of 164 breast cancer patients were included.

For **(objective 4)** retrospective study was conducted in order to determine the survival of breast cancer patients who were followed up from September 2010 to August 2014. The minimum sample size was calculated based on open epi by assuming:

α is Type I error rate = 95%

Power = Type II error rate =80%

q_1 = Proportion of subjects that are in Group 1 (exposed), 5 year survival rate of breast cancer patients in stage III =0.33. [113].

q_0 = Proportion of subjects that are in Group 0 (unexposed); which is 5 year survival rate of breast cancer patients in stage I and stage II= $1-q_1$ =0.67.

Ratio of unexposed to exposed (Group 1/Group 0) = which is assumed to be 1

The calculated minimum total sample size was = 76 (38 exposed and 38 unexposed)

However, to maximize our sample size and power of the study, a total of 402 women were included in the study.

4.5. Study variables

Objectives	Dependent variables	In dependent variables
Objective 1	Sociodemographic and Hematologic profile	Age, Education, Occupation, Income, RBC, WBC, HB, Platelet, PCV, ABO/ Rh blood type
Objective 2	Breast cancer status	Sociodemographic factors (sex, age, education, marital status...) RH factors (age at first birth, age at menarche, OC use). Life style factors: (Smoking, alcohol consumption, obesity, inactivity Other factors: (family history, previous benign breast surgery,)
Objective 3	Chemotherapy Adherence	Sociodemographic factors, distance from referral center, severity/advanced stage of disease.
Objective 4	Survival of BC patients	Sociodemographic factors, Clinical factors(Tumor size, Stage of disease at diagnosis

4.6. Survey instruments and Data collection

4.6.1. Survey instruments

Data collection tools were developed based on a review of similar literature conducted on breast cancer. For **objectives 1 and 2**, a structured questionnaire was administered to each individual to collect information on identification data, socio-demographic profile, reproductive factors, and other risk factors. In addition, a checklist was also developed to collect the laboratory results of the hematological profile and blood group. For measurement of adherence and survival **(objectives 3 and 4)**, structured questionnaires and checklists were prepared from different literature. For **objectives 1 and 2**, initially the questionnaire was prepared in English and then translated to the local language, Amharic. Data collection tools were pre-tested, and appropriate modifications were made.

4.6.2. Data collection procedures

In general, data collection procedures included structured interviews, anthropometric measurement, blood specimen collection, and patient card review. In order to collect all those data, different data collectors, including BSc or clinical nurses, oncology nurses, laboratory professionals, and oncology residents, were participated. Regarding the case-control study **(objectives 1–3)**, prior to data collection, written informed consent was obtained from each study participant. The height and weight of each study participant were measured by a standardized meter and weight measures. Hematological parameters of breast cancer patients were recorded from their laboratory reports and patient cards. Eligible controls were selected by breast physical examination, which was done by female oncology residents. The interview was conducted by four experienced BSc or clinical nurses. Blood samples were collected from selected controls by experienced medical laboratory professionals at the end of each interview. Finally, the collected blood sample was analyzed at TASH Laboratory using a Sysmex KX-21N hematology analyzer.

For **objective 3**, assessment of adherence to chemotherapy, after eligible participants were identified based on the required criteria, data were collected at one point in time by two trained oncology nurses during the 3^{rd}, 5^{th} , and 7^{th} cycles, depending on the type of treatment regimen, because these cycles are closer to the final recommended or planned cycle. In addition, card reviews and telephone interviews were also conducted in order to get complete data.

On the other hand, in order to collect survival data for **objective 4**, a structured checklist was prepared based on predetermined patient records. Data were collected for patients who had been diagnosed from September 2010 to August 2014 at TASH. This secondary data were collected by trained and experienced oncology resident.

In addition, phone calls were made to assess the patient's treatment status and confirm whether the patient was alive or not. The phone interview was made between patients and their close relatives, especially for patients who were dead. Finally, the reported status of each patient was recorded. After that, phone calls were made, and those patients whose phones did not respond after three repeated calls were excluded from the analysis. The entire data collection process was supervised by the principal investigator.

4.6.3. Laboratory procedure

Blood specimen collection and analysis

As indicated in the above section, in order to avoid repeated puncture of patients, blood specimens were not collected for breast cancer patients since they have hematology laboratory results in their records. In this case, the recent hematology laboratory result was used. The laboratory tests were conducted at Tikur Anbessa Hospital Laboratory. For control groups, after all study participants completed a detailed questionnaire, about 4 milliliters of venous blood were collected with an EDTA test tube to test the ABO blood group and hematological parameters, including hemoglobin, PCV, WBC, RBC, platelet count, different components of WBC, RDW, and red cell indices (MCV, MCH, MCHC). The estimation of parameters was done by the Sysmex Automated Hematology Analyzer Kx-21. The Sysmex KX-21 is an automatic multi-parameter blood cell counter for clinical laboratories. The KX-21 processes approximately 60 samples per hour and displays the particle distribution curves of WBC, RBC, and platelets on the LCD screen, along with data for 18 parameters, as the analysis results. The KX-21 employs three detector blocks and two kinds of reagents for blood analysis. The WBC count was measured by the WBC detector block using the DC detection method. The RBC count and platelets are taken by the RBC detector block, also by using the DC detection method. The HGB detector block measures the hemoglobin concentration using the non-cyanide hemoglobin method [121].

ABO and RH blood grouping

The determination of the ABO blood group is defined by demonstrating the presence or absence of antigens A and/or B on the surface of human red blood cells and by detecting the presence or absence of anti-A and/or anti-B antibodies in the plasma. The presence or absence of the D antigen is determined by testing the red blood cells with anti-D [122].

4.7. Operational definition

The ABO blood group system is a system used to group human blood into different types based on the presence or absence of certain markers on the surface of red blood cells. The four main blood types are A, B, O, and AB.

The Rh blood group system is a system for classifying blood groups according to the presence or absence of the Rh antigen, often called the Rh factor, on the cell membrane of the red blood cells.

Rh-positive: If the red blood cells contain antigen, they are referred to as Rh-positive.

Rh negative: If the red blood cells do not contain antigen, they are referred to as "Rh negative."

Age at Menarche: Age at menarche is defined as the age at which the first menses occurred, as reported by the respondents.

Age at first live birth: Age at first live birth refers to the age when the first full-term birth occurred.

Abortion: Abortion is the termination of pregnancy before 28 weeks of pregnancy.

Parity: Parity is the number of pregnancies that a participant had.

First-degree family history of breast cancer: First-degree family history of breast cancer was defined as women who had sisters, mothers, or daughters with breast cancer.

Menopausal status: Women were classified as menopause if they had not menstruated during the past one year before the date of data collection.

Previous benign breast surgery: Previous benign breast surgery refers to whether women had surgery for a non-cancer lump.

Body Mass Index (BMI): BMI is categorized based on WHO classification as underweight (BMI < 18.5), normal weight (BMI =18.5-24.9), pre obesity (BMI = 24.9–29.9), and obesity (BMI >29.9).

Consumption of food items: (vegetable, fruit, meat, and milk intake) is defined as the frequency of weekly intake of specific food items.

A "cigarette smoker" is a woman who smokes cigarettes regularly, at least one cigarette per day for three months or longer.

Alcohol drinker: is defined as a woman who consumes alcohol (such as beer, wine, or hard liquor, including local drinks and mixed drinks) regularly, that is, at least once per week for six months or longer.

Moderate exercise is defined as women participating in moderate activities or sports (e.g., walking, golf, and volleyball, cycling on Level Street; recreational tennis or softball).

Strenuous exercise: refers to women's participation in strenuous activities or sports (e.g., swimming, running, aerobics).

Clinical stage at diagnosis was assigned to each patient (as stage I, stage II, stage III, and stage IV) based on the American Joint Committee on Cancer Tumor, Node, and Metastasis (TNM) classification scheme for staging breast cancer.

Histological grade: A description of a tumor based on how abnormal the cancer cells and tissue look under a microscope and how quickly the cancer cells are likely to grow and spread.

Tumor size: It is defined as the maximal size of the invasive component of the primary tumor on pathologic examination.

Adherence: "A patient is considered adherent if they take 80% of their prescribed medication. (The American Medical Association).

Non adherence: If patients take less than 80% of their prescribed medication, they are considered non-adherent. (The American Medical Association).

Overall survival (OS) was defined as the duration of time from the date of initial diagnosis until the date of death from any cause, the date lost to follow-up, or the end of the study.

4.8. Study variables and measurement

For **all objectives (1-4),** the place of residence was categorized as urban or rural. The age of participants at diagnosis was categorized into four categories: less than 40, 40–49, 50–59, and 60 years and above based on the American Cancer Society [123]. Marital status is divided into single, married, divorced, or widowed. Education level was categorized into illiterate, read and write, primary (1-8), secondary (9-12), college diploma, and above. Occupation was categorized as housewife, government employee, private (private company, merchant), and other (daily laborer, house made). Monthly income was categorized based on the calculated median income as less than 2000 Ethiopian birr and 2000 Ethiopian birr and above.

For **objective 1** sociodemographic and hematologic profiles were measured using previous studies and guidelines. In order to assess the presence of selected hematologic abnormalities, the reference range was taken from the output of the CBC SYSMEX KX-21N hematology analyzer. In addition, the severity of anemia was categorized based on WHO 2011 hemoglobin (HB) concentration for the diagnosis of anemia and assessment of severity [124]. As per this assessment, if HB concentration was $\geq$12gm/dl, there was no anemia; there was mild anemia when HB was 11.0-11.9gm/dl, moderate anemia when HB was 8.0-10.9 gm/dl and severe anemia when HB was less than 8gm/dl.

Moreover, anemia was also further characterized as microcytic and macrocytic, based on MCV values, and hypochromic and normochromic anemia, based on MCHC values. In addition, leukocyte and platelet values were characterized based on the reference range of the hematology analyzer. When the WBC count was less than 3.7 x 10^9/L, it was characterized as leucopenia, whereas when the value was greater than 10.4 x10^9/L, it was characterized as leukocytosis. Regarding the platelet count, if the value was less than 140 x 10^9/L, it was characterized as thrombocytopenia, whereas when the value was greater than 385 x 10^9/L, it was characterized as

thrombocytosis. ABO/Rh blood grouping. ABO/Rh blood grouping was done using the slide agglutination method using commercially available antisera (anti-A, anti-B, and anti-D).

For **objective 2**, sociodemographic, anthropometric, lifestyle, and reproductive factors were assessed as study variables.

BMI was calculated by dividing weight (kg) by the square of height (m) and categorized based on WHO classification as underweight, normal weight, pre-obesity, and obesity. Consumption of food items: (vegetables, fruits, meat, and milk intake) was calculated per week as "once a week or less and more than once a week. Smoking habit (yes or no) and alcohol consumption were categorized as (no drinker, 1 glass per week or less," and more than 1 glass per week). Consumption of solid oil at room temperature was categorized as "yes" or "no." The sources of fuel were categorized as electric, wood/animal dung, charcoal/kerosene, and combinations. Strenuous exercise (such as swimming) and moderate exercise (such as walking) were categorized as "no exercise, less than 5 hours per week," and 5 hours and above per week."

Age at menarche was categorized as < 12 years, 12–15 years, and >15 years. Family history of breast cancer, oral contraceptive use, and previous breast surgery were categorized as "yes" or "no." Menopausal status, (premenopausal, postmenopausal) and number of live births (1-3, live birth, 4-6, and > live birth. Abortion (no abortion, one abortion, and two or more)

For **objective 3,** even though a total of 230 patients were identified as a study population, 24 (10.4%) patients were excluded due to incomplete information, and they have opted for other forms of treatment rather than chemotherapy. In addition 7(3.0%) patients were considered ineligible because they were moved to other regional chemotherapy centers and private health facilities, since it was difficult to access patients as well as their record to get the necessary information. Moreover, 17 (7.3%) were also excluded because those patients planned for chemotherapy but did not start their treatment due to unknown reasons. Similarly, 18 (7.8% of patients were ineligible because they died before the initiation of chemotherapy and during the follow-up period. Finally, a total of 164 women with breast cancer were included in this analysis. A patient was considered as non-adherent if they did take less than 80% of their prescribed therapy and if they did not present for two consecutive doses of chemotherapy. Patients who had

dose reduction and/or omission due to an inadequate hematological profile or poor clinical condition, unplanned public holidays were not included as non-adherent. The patients or patients' family members were contacted via phone calls to supplement the collected data.

For **objectives 3 and 4**, clinical stage at diagnosis was assigned to each patient based on the American Joint Committee on Cancer Tumor, Node, and Metastasis (TNM) classification scheme for staging breast cancer [125]. Accordingly, the stage at diagnosis was categorized as (stage I, Stage II, stage III, and stage IV). Histological grade of breast cancer was categorized into three grades (1-well differentiated, 2 moderately differentiated, and 3-poorly differentiated) by using the Nottingham Grading System [126]. Tumor size was categorized in accordance with the American Joint Committee on Cancer (AJCC) guidelines (<2 cm, 2–5 cm, >5cm) [127]. The date of first diagnosis was obtained from a patient's pathology report. Patient status (death or alive) was obtained from patient records and phone calls. Overall survival was measured from the date of diagnosis to the last date of follow up or death due to all causes.

4.9. Data management and analysis

After data collection was completed, the collected data were coded, and double data entry was done using EPI-INFO statistical software. The data were cleaned and exported to the Statistical Package for Social Science (SPSS). The data were analyzed by SPSS version 20 software. Then, a descriptive analysis was made to assess the socio-demographic characteristics of the study participants. Numeric data was checked for normality by using a normality plot (Q-Q plot). A transformation was made for variables that did not have a normal distribution. A mean with a standard deviation was used for variables with a normal distribution. A median with an interquartile range was used for the squid distribution. In all multivariable analyses, multicollinearity was checked using variance inflation factors (VIF < 10) as a cutoff point. The goodness of fit test was checked using the Pearson Chi square test. Fisher exact tests were also performed when the assumption of the chi square test was violated. Study variables that have a P value <0.25 on bivariate analysis were included for multivariable analysis. The strength of the association was finally evaluated using the adjusted odds ratio and its 95% confidence interval. Variables with a P-value less than 0.05 were taken as statistically significant when looking for associations between dependent and independent variables.

For **objective 1**, an independent student t-test was used to compare the mean and standard deviation of different hematological parameters. In addition, a Chi-square test was conducted to identify significant differences in sociodemographic characteristics and hematological parameters between cases and controls. For risk factor analysis **(objective 2),** bivariate and multivariable logistic regression analysis was conducted in order to see the association between breast cancer and sociodemographic, lifestyle, and reproductive factors.

Concerning the measurement of adherence for chemotherapy **(objective 3),** a descriptive analysis was done. A Chi-square test was also conducted in order to assess significant differences between adherence and independent variables. For factors associated with adherence, an analysis was made based on baseline characteristics. Due to the smaller sample size, the number of non-adherence cases was limited, and further analysis, including binary and multivariate analysis, was not made.

Survival **(objective 4)** was calculated as the time difference in months between the date of diagnosis and the date of death during the follow-up period. Patients who remained alive until the last follow-up were censored. In this case, the censor date for patients who remained alive was the date of the phone call that confirmed their status. Based on life table analysis, one, three, five, and ten-year overall survival was calculated. Median survival estimates were obtained using the Kaplan-Meier survival analysis method. Survival curves were compared using the log-rank statistic. Bivariate and multivariable analyses were performed using Cox's proportional hazards model. The results of the Cox proportional hazard model are presented as hazard ratios along with their 95% confidence intervals. The proportional hazard assumption was checked using graphical methods.

4.10. Data Quality Control and Quality Assurance

In order to maintain the quality of the data, different quality assurance techniques were applied. In order to minimize errors when using hospital controls, healthy controls were selected after a breast physical examination was made. In order to facilitate understanding, a questionnaire was prepared in English and translated into Amharic. For those who did not speak Amharic language, caregivers and nurses were used as translators.

The entire data collection instrument was pretested, and appropriate modifications were made. The data were collected by trained and experienced nurses, laboratory professionals, and oncology residents. Daily supervision was made of all questionnaires collected each day. During supervision, each questionnaire was checked for completeness and for holding appropriate information. If there were unfilled or missed questions during data collection, appropriate corrections were made. Appropriate statistical models were applied for each study variable to maintain the quality of the findings. The laboratory analysis was performed in a highly controlled environment, which means the performance of the machine is checked before analyzing a patient sample by using quality control materials, the instruments are calibrated, and the personnel are experienced medical laboratory professionals specializing in hematology and immunohematology. All collected blood specimens were analyzed on the same day of sample collection. Quality control samples were analyzed before testing actual patient samples in order to check the performance of the testing reagents and the machine/analyzer to maintain the quality of the test.

4.11. Ethical considerations

Ethical approval was obtained from the School of Public Health Research Ethical Review Committee and Addis Ababa University, College of Health Sciences Institutional Review Board with protocol number 073/17/SPH. Permission was obtained from the Oncology Department of TASH. Written informed consent was obtained from each respondent. Confidentiality and privacy were maintained throughout the study. During the selection of controls, a breast physical examination was made by a female physician. During a physical examination, women who had breast masses were consulted, and their results were given for free in order to get an early diagnosis and treatment. Confidentiality and privacy were well maintained throughout the study. Regarding the survival study, a waiver of consent was secured from the college IRB to extract secondary data from patients' records. Confidentiality was ensured by removing any details that might identify any patient or their family. This study was conducted based on research requirements, regulations, and policies that safeguard the wellbeing of study participants and ensure the reliability and integrity of this finding. Therefore, all methods were carried out in accordance with relevant guidelines and regulations.

Summary of study design, population and study period

As indicated above, in order to address the study objectives, different study designs were used. The following table gives a summary of the study design, population, and study period for this study (Table 1).

Table 1. Summary of the Breast Cancer Study Design, Population, and Sample Size at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018–2021.

Paper	Topic	Study design	Study population	Sample size
I	Socio-demographic and Hematological Determinants **(Objective 1)**	Hospital based case control study	Newly diagnosed breast cancer patients and female care givers.	460 (230 cases and 230 controls)
II	Frequency and association of ABO/Rh blood group. **(Objective 1)**	Hospital based case control study	Newly diagnosed breast cancer patients and female care givers.	421 (191* cases and 230 controls)
III	Risk Factors associated with breast cancer **(Objective 2)**	Hospital based case control study	Newly diagnosed breast cancer patients and female care givers.	460 (230 cases and 230 controls)
IV	Level of adherence to chemotherapy. **(Objective 3)**	Hospital based cross sectional study	Breast cancer patients treated with chemotherapy.	164 BC patients
V	Survival of Breast Cancer Patients. **(Objective 4)**	Retrospective cohort study	Breast cancer patients treated from September 2010 to August 2014.	402 BC patients

Since 39 cases did not have blood group in their records, they were excluded from analysis.

5. Results

The main findings of this dissertation research are based on five different studies as speculated in the specific objective. The first study objective is about socio-demographic and hematological determinants of Breast Cancer. This study also identifies the profile and association of ABO/Rh blood group with breast cancer. Moreover, this study also assesses potential risk factors associated with breast cancer. Chemotherapy adherence levels and associated factors were also identified. Finally, survival of breast cancer patients were also determined (Table2).

Table 2. Summary of main findings of the dissertation by specific objectives, TASH, Addis Ababa, Ethiopia, 2018-2021.

Papers	Topic	Main findings
I	Socio-demographic and Haematological Determinants	Most of the participants, 174 (75.7%) were urban residents, 143, (62.2%) were < 40 years of age, (67.4%) were married and 34 (14.8%) were illiterate. Most of hematological parameters were significantly lower among breast cancer patients.
II	ABO/Rh blood group & BC	Majority of cases and controls were O^+ blood group. Significant association was not found between ABO/Rh factors with breast cancer.
III	Factors associated with BC	Women, who were unemployed, consumed solid oil, using wood/animal dung as fuel source, post-menopause; with previous benign surgery & early menarche, (<12 years) had significantly higher odds of BC, while, it is significantly lower among women who had moderate physical activities.
IV	Chemotherapy adherence	Level of chemotherapy adherence was 83.5% (137/184). Sever illness was the main identified reasons for non-adherence. In addition, treatment regimen and distance from referral center were significantly associated with non-adherence.
V	Survival of BC patients.	Of the 402 patients, at the end of follow up, 169, (42%) patients were alive and 233, (58%) of patients were dead. The survival rate was poor and it was worse, in patients with late stage at diagnosis and with metastasis tumor.

5.1. Sociodemographic and hematologic profile of breast cancer patients (Paper I)

5.1.1. Socio demographic characteristics of study participants

In this study, 230 cases and 230 controls were included. Based on administrative regions, majority 82, (35.7%) of cases were from Addis Ababa, followed by Ormia region, which contribute for 68, (29.6%) of the cases. In addition, there were cases from Tigray, Somali, Afar and other regions. The majority (70.9%) of the cases and 75.7% of the controls were urban dwellers. The mean ages of were 42.8 $\pm$ 12.1 and 39.3 $\pm$ 11.1 years (P =0.089) for cases and controls, respectively. More than half, 125 (54.3%) of cases and 143(62.2%) of controls were less than 40 years old. The majority (76.1%) of cases and 67.4% of controls were married. However, nearly half, one hundred (43.5%) of the cases were illiterate or had no formal education, while 30% of the controls had attained secondary education. More than two-thirds (69.6%) of the cases and 43.1% of the controls were housewives. Even though a limited number of study participants replied about their income, 37 (34.3%) of the cases and 16 (12.6%) of the controls earn less than 1000 Ethiopian Birr per month. Based on the result of the Pearson Chi-square test, there was no significant association between breast cancer and place of residence (P = 0.247), age (P = 0.089), or marital status (P = 0.110). However, educational status, income, and occupation were significantly associated with breast cancer (P<0.001) (Table 3).

Table 3. Socio demographic characteristics of Study participants at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018-2021. (n=460)

Variables	**Cases (n = 230)**		**Controls (n = 230)**		**P Value**
	Frequency	**Percent**	**Frequency**	**Percent**	
Administrative region					
Addis Ababa	82	35.7	92	40.0	**0.002**
Oromia	68	29.6	73	31.7	
SNNP	29	12.6	26	11.3	
Amhara	21	9.1	32	13.9	
Other	30	13.0	7	3.0	
Resident					
Urban	163	70.9	174	75.7	0.247
Rural	67	29.1	56	24.3	
Age group (years)					
<40	125	54.3	143	62.2	0.089
40 and above	105	45.7	87	37.8	
Mean age (Mean ±SD)	42.83 ± 12.06		39.33 ± 11.14		
Marital status					0.110
Single	23	10.0	29	12.6	
Married	175	76.1	155	67.4	
Divorced/widowed	32	13.9	46	20.0	
Education level					**< 0.001**
Illiterate	100	43.5	34	14.8	
Read and write	26	11.3	9	3.9	

Primary education	33	14.3	56	24.3	
Secondary education	45	19.6	69	30.0	
College and University	26	11.3	62	27.0	
Occupation					**< 0.001**
House wife	160	69.6	99	43.1	
Government employee	34	14.8	70	30.4	
Private	28	12.1	42	18.2	
Other	8	3.5	19	8.3	
Monthly income (Birr)	(N=108)		(N=127)		**< 0.001**
< 2000	69	63.9	53	41.7	
2000 and above	39	36.1	74	58.3	

5.1.2. Hematologic profile of breast cancer cases and controls

Hemoglobin, Red Blood Cell, Platelet count and Packed Cell Volume

Based on independent t test, the overall mean values with standard deviation of HB, RBC, PCV, of cases were (13.1 $\pm$ 1.6g/dl, 4.6 $\pm$ 0.53x 10^{12}/L and 38.7$\pm$ 4.5 %, respectively and those values for controls were (14.0$\pm$1.3g/dl, 4.8 $\pm$ 0.47 x 10^{12}/L, 40.5 $\pm$ 3.5% respectively. Based on this finding, the mean value of HB, RBC, PCV, of breast cancer patients were significantly lower than the controls. On the other hand, mean platelet count for the cases was significantly higher than (323. 4 $\pm$ 108.1x10^9L) the controls (282.0$\pm$ 70.0 x 10^9L). In addition, the mean value of total WBC was 7.1$\pm$ 2.8 and 7.1 $\pm$ 2.4 x 10^9/L for cases and controls, respectively. Based on this finding there was no significance difference in mean total WBC count between cases and controls (Table 4).

Table 4. HB, RBC, platelet count and PCV parameters of cases and controls at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018-2021, (n=460)

Parameter	Cases	Controls	P – Value
HB (Mean ± SD) g/dl	13.1 ± 1.6	14.0± 1.3	< **0.001**
Minimum HB	8.7	7.3	
Maximum HB	16.4	20.1	
RBC (Mean ± SD) x 10^{12}/L	4.6± 0.54	4.8±0.5	**0.020**
Minimum RBC	2.8	3.4	
Maximum RBC	6.2	7.1	
WBC (Mean ± SD) x 10^{9}L	7.1 +2.8	7.1+2.4	0.960
Minimum WBC	2.0	2.9	
Maximum WBC	20.1	17.1	
Platelet (Mean ± SD) x 10^{9}L	323. 4± 108.1	282.0± 70.0	< **0.001**
Minimum Platelet	110.0	119.0	
Maximum Platelet	827.0	469.0	
PCV (Mean ± SD) %	38.7± 4.5	40.5 ± 3.5	< **0.001**
Minimum PCV	26.2	24.8	
Maximum PCV	49.2	58.4	

Key= PCV= Packed Cell Volume; RBC Red Blood Cells, HB= Hemoglobin; P= P- value for Independent t test

Red cell induces

The overall MCV, MCH and MCHC values of the cases and controls were (84.3±8.1fl, 29.0±4.2pg, and 33.6±1.7 %,) and (85.7 ±6.0 fl, 29.5±2.4 pg, 34.2± 2.5%), respectively (Table 5). As indicated in Table 5, MCV and MCHC values were significantly lower among breast cancer patients, ($P < 0.05$). However, there was no significant difference between cases and controls in their mean MCH value (Table 5).

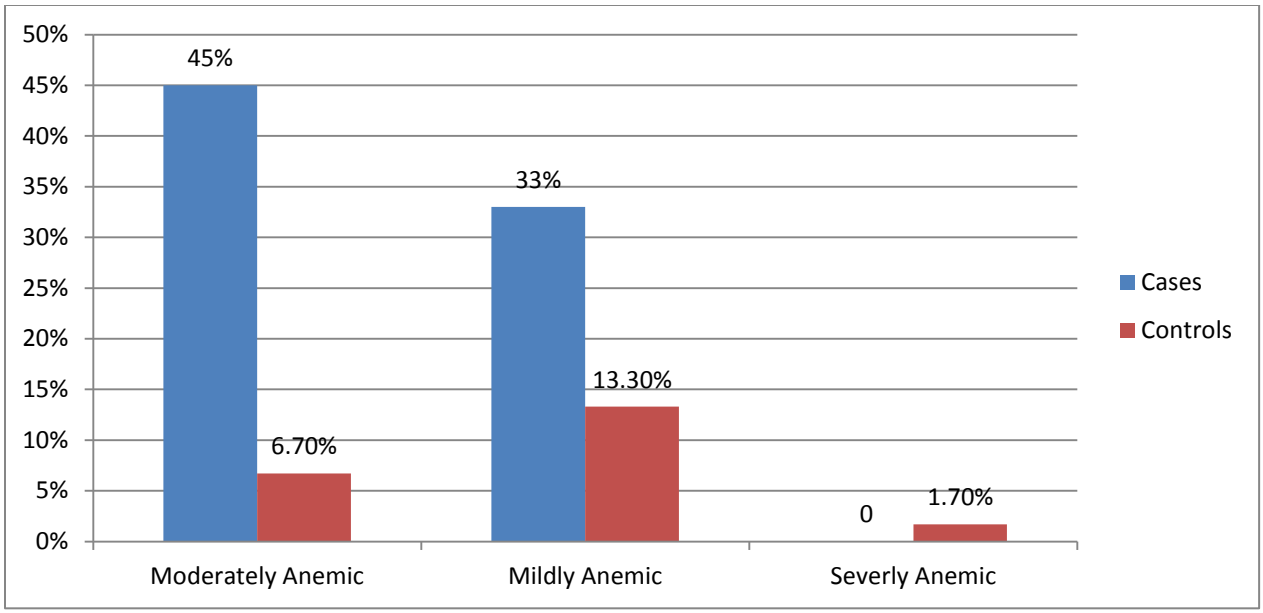
Table 5. Red cell indices values of study participants at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018-2021, (n=460)

Red cell indices parameters	Cases	Controls	P- value
MCV, fl (Mean ± SD)	84.3 + 8.1	85.7 +6.0	**0.042**
Minimum MCV	65.6	62.4	
Maximum MCV	105.9	111.5	
MCH, pg (Mean ± SD)	29.0 + 4.2	29.5+2.4	0.153
Minimum MCH	21.2	19.3	
Maximum MCH	37.5	39.2	
MCHC, gm/dl (Mean ± SD)	33.7 + 1.7	34.2 + 2.5	**0.005**
Minimum MCHC	22.4	29.4	
Maximum MCHC	38.5	36.6	

Key= MCV = Mean Cell Volume MCH= Mean Cell Hemoglobin, MCHC= Mean Cell Hemoglobin Concentration, SD= Standard Deviation, fl = femtoliter, pg = pico gram

Characterization of some selected hematologic parameters

In this study, based on their hemoglobin values, among a total of 230 cases, 47 (20.4%) were anemic. On the other hand, out of 230 controls, 13 (5.6 %) of them were anemic. Moreover, based on severity of anemia, the majority, 27 (11.7%) of cases and 4 (1.7%) controls, were moderately anemic. In addition, 20 (8.7%) of cases and 8 (3.5%) of controls were mildly anemic ($P < 0.001$) (Table 6). Moreover, out of the total 60 anemic study participants, 20 (33.3%) were cases and 8 (13.3%) were controls were mildly anemic. In addition, 27(45%) of cases and 4 (6.7%) of controls were moderately anemic and only one control (1.7%) were severely anemic (Figure 2).



Classification of Anemia: When HB<12gm/dl, (Mild anemia when HB is 10.9-11.9 gm/dl, Moderate anemia, when HB is 8.0-10.9 gm/dl, and Severe anemia when HB is <8 gm/dl)

Figure 2. Severity of anemia among breast cancer cases and controls at Tikur Anbessa Specialized Hospital, Addis Ababa, 2018-2021 (n=60)

Based on the chi square test, microcytic anemia was found in 64 (28.2%) of the cases and 42 (18.4%) of the controls. However, macrocytic anemia was found in 2 (0.9%) of cases and 3 (1.3%) of controls. Similarly, 15(6.6%) of cases and 8 (3.5%) of controls had hypochromic anemia. In addition, 23 (10.5%) of cases and 7 (3%) of controls had normocytic anemia, 27 (11.7%) of cases and 9 (3.9%) of controls had normochromic anemia, and 9 (3.9%) of cases and 4 (1.7%) of controls had microcytic hypochromic anemia. Thrombocytosis was found among 54 (23.5%) of the cases and 18 (7.8%) of the controls ($P < 0.001$). The finding also indicated that 16 (7.0%) of cases and 1 (0.4%) of controls were both anemic and had thrombocytosis ($P < 0.001$). Similarly, 2.2%) of cases and none of the controls had the triple burden of anemia, lecocytosis, and thrombocytosis (Table 6).

Table 6: Distribution of abnormal hematological values among breast cancer cases and controls at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2019.

Parameters	**Cases**		**Controls**		**X^2**	**P – value**
Hemoglobin (gm/dl)	N	%	N	%		
12 and above (No anemia)	183	79.6	217	94.3		
Mild anemia	20	8.7	8	3.5	26.09	< **0.001**
Moderate anemia	27	11.7	4	1.7		
Severe anemia	0	0	1	0.4		
Microcytic anemia	64	28.2	42	18.4		
Macrocytic anemia	2	0.9	3	1.3	6.2	0.046
Hypochromic anemia	15	6.6	8	3.5	2.24	0.134
Normocytic anemia	23	10.0	7	3.0	9.13	**0.003**
Normochromic anemia	27	11.7	9	3.9	9.76	**0.002**
Microcytic Hypochromic	9	3.9	4	1.7	1.97	0.159
Leucopenia	13	5.7	9	3.9	0.76	0.681
Normal	198	86.1	202	87.8		
Lecucytosis	19	8.3	19	8.3		
Thrombocytopenia	4	1.7	5	2.2		
Normal	172	74.8	207	90	21.9	< **0.001**
Thrombocytosis	54	23.5	18	7.8		
Both anemic and thrombocytosis	16	7.0	1	0.4	13.7	< **0.001**
Both anemic , thrombocytosis and lecucytosis	5	2.2	0	0.0	5.05	**0.025**

**** P= Pvalue for X2 test. The reference range is based on the WHO classification of anemia. Regarding leucocyte and platelet, the reference range is based on the established range of the CBC Sysmex KX – 21N hematology analyzer***

****Anemia, When HB<12gm/dl, (Mild anemia when HB is 10.9-11.0 gm/dl, Moderate anemia when HB is 8.0-10.9 gm/dl, and Severe anemia when HB is <8 gm/dl). * Lecucytosis: when total WBC count is >10.4 x 10^9/L, Leucopenia: when total WBC count is < 3.7 x 10^9/L.***

5.1.3. Blood group profile of breast cancer patients (Paper II)

Sociodemographic characteristics of study participants

In this study, a total of 421 study participants (191 cases and 230 controls) were enrolled in order to assess the frequency and association of the ABO/Rh blood group with breast cancer. Based on place of residence, the majority, 131 (68.6%) of cases and 174 (75.7%) of controls, were urban residents. The mean age was 43.06 ± 12.3 and 39.44 ± 11.0 years for cases and controls, respectively. Regarding marital status, 173 (90.6%) of cases and 201 (87.4%) of controls were married. Nearly half, 84 (44%), of cases were illiterate, while only 34 (14.8%) of controls were illiterate. On the other hand, more than half, 130 (69%) of cases, and nearly half, 99 (43%) of controls, were unemployed (Table 7).

Table 7. Socio demographic characteristics of study participants at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018-2021, (n=421)

Variables	**Case (n=191) N (%)**	**Control (n=230) N (%)**
Residence		
Rural	60 (31.4)	56 (24.3)
Urban	131 (68.6)	174 (75.7)
Age group (years)		
<40	89(46.6)	136 (59.1)
40–49	46 (24.1)	45 (19.6)
50-59	32(16.8)	36(15.7)
60 and above	24 (12.6)	13 (5.7)
Mean ± SD) (year)	43.06 ± 12.3	39.44 ± 11.0
Marital status		
Single	18(9.4)	29(12.6)
Married	150(78.5)	155(67.4)
Divorced/widowed	23(12.1)	46(20.0)
Education level		
Illiterate	84(44.0)	34(14.8)
Read and write	20(10.5)	9(3.9)
Primary education	26(13.6)	56(24.3)
Secondary education	37(19.4)	69(30.0)
Diploma and above	24(12.6)	62(27.0)
Occupation		

House wife	130(68.1)	99(43.1)
Government employee	30(15.7)	70(30.4)
Private	23(12.0)	42(18.2)
Other	8(4.2)	18(8.3)
Monthly income (Birr)	N=89	N=127
> 2000	58(65.2)	53 (41.7)
2000 and above	31(34.8)	74 (58.3)

Frequency of ABO/Rh blood group of study participants

In this study, the majority, 89 (46.6%) of cases and 96 (41.7%) of the controls, had the O blood group. Blood group AB was the least common, with 19 (9.9%) and 20 (8.7%) among cases and controls, respectively. The occurrence of the ABO blood group among both cases and controls was in the order O > A >B > AB. Significant association was not found between the ABO blood group and breast cancer. In addition, majority, 177 (92.7%) of cases and 214(93.0) of controls) were Rh positive. Similarly, there was no significant difference between cases and controls in Rh positivity; 117 (92.7%) of cases and 214 (93.0%) of the controls were Rh positive (Table 8).

Table 8. Distribution of ABO/Rh Blood groups of breast cancer cases and controls at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018-2021. (n=421)

Factors	**Case**		**Control**		**X^2**	**P- Value**
	No	**%**	**No**	**%**		
ABO blood group					1.59	0.662
A	45	23.6	63	27.4		
B	38	19.9	51	22.2		
AB	19	9.9	20	8.7		
O	89	46.6	96	41.7		
Rh blood group					0.022	0.882
Rh positive	177	92.7	214	93.0		
Rh negative	14	7.3	16	7.0		

As shown in Figure 3, the frequency of ABO/Rh blood groups was almost the same among cases and controls when combining ABO and Rh types. This study found that the majority; (86, or 45%) of cases and 91, (39.6%, of controls were O+. It was also found that 37 (19.4%) of cases and 58 (25.2%) of controls were A+. Even though A blood group was found to be higher among control groups, the difference was not statistically significant.

In addition, 37 (19.4%) of cases and 47 (20.4%) of controls were B+. On the other hand, only 3 (1.6%) of cases and 5 (2.2%) of controls were O-negative. However, AB negative is the least common blood type for both groups (about 1.0%) (Figure 3).

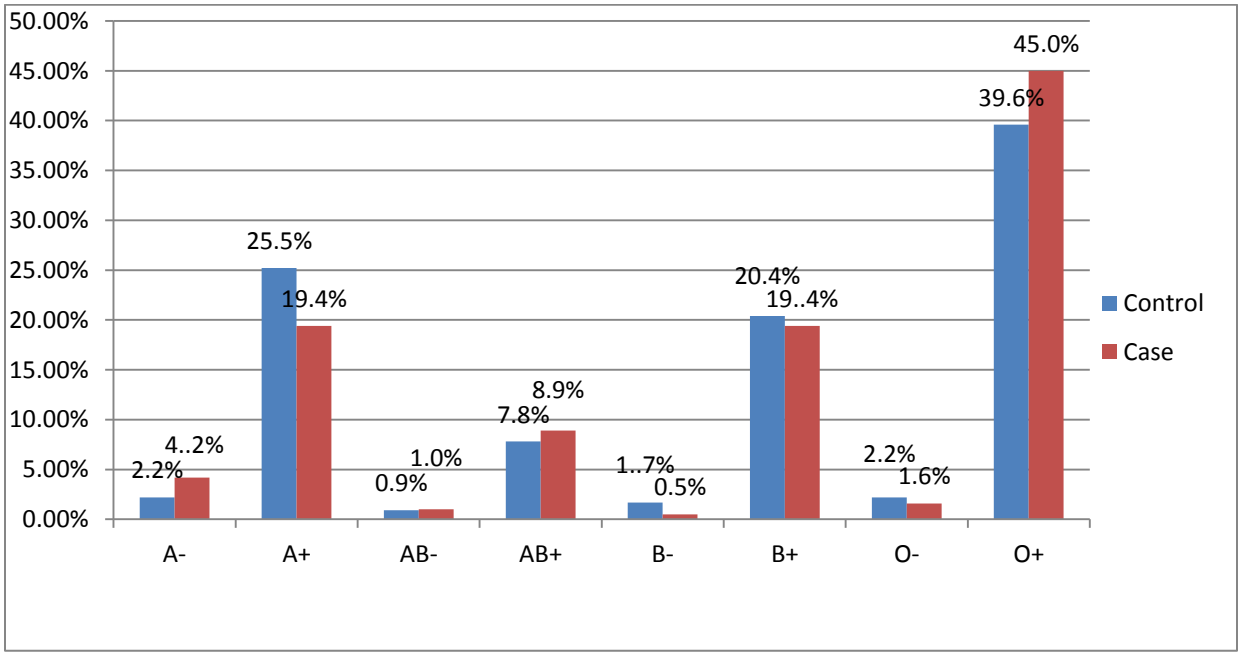


Figure 3. ABO/Rh blood groups frequencies of breast cancer cases and controls at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018-2021, (n=421).

5.2. Risk factors for breast cancer patients (Paper III)

5.2.1. Sociodemographic characteristics associated with breast cancer

In order to assess the factors associated with breast cancer, a total of 230 breast cancer cases and 230 healthy controls were participated. The mean age (± SD) was 42.83 ± 12.06 for cases and 39.33 ± 11.14 years for controls. Based on the result of bivariate analysis, the odds of breast cancer were significantly higher among women aged 40–49 and >60 years. However this association is declined after multivariable logistic regression analysis was conducted. It was also found that the odds of developing breast cancer among illiterate women were 4.43 times higher (95% CI 2.83–9.94, P< 0.001) compared to literate women. Similarly, the odds of breast cancer were also 3.03 times higher (95% CI: 1(2.06-4.44) P < 0.001) among unemployed women as compared to employed women. Regarding income, the odds of breast cancer were 2.43 times (95% CI: 1.43–4.14, P < 0.001) higher among women with a monthly income of 2000 Ethiopian Birr compared to women with a monthly income of >2000 Ethiopian Birr. Though, there was no significant association between breast cancer, place of residence, or marital status. On the other hand, the odds of breast cancer were 0.26 times lower among obese women (Table 9).

In order to eliminate the effect of confounding variables, multivariable analysis was conducted by selecting variables with a P value ≤ 0.25 during bivariate analysis. The finding indicated that the odds of breast cancer were 3.78 times higher (95% CI: 1.46–9.78, p = 0.006) among unemployed women. It was also found that the odds of breast cancer were higher among illiterate women (2.57 95% CI, 1.38-4.79, P = 0.003). Similarly, the odds of breast cancer were 0.19 times lower among obese women as compared to underweight women. However, the association between breast cancer and age and monthly income declined after multiple logistic regression models were applied for confounding variables (Table 9).

Table 9. Socio demographic characteristics and anthropometric associated with breast cancer cases at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018-2021, (n=460)

Variables	Case N (%)	Control N (%)	Bivariate analysis		Multivariable analysis	
			COR (95% CI)	P-value	AOR (95% CI)	P-value
Residence						
Rural	67 (29.1)	56 (24.3)	1:00		1:00	
Urban	163 (70.9)	174 (75.7)	0.783(0.52-1.19)	0.247	1.73-(0.78-3.84)	0.176
Age group (years)						
<39	106 (46.1)	136 (59.1)	1:00		1:00	
40–49	58 (25.2)	45 (19.6)	1.65(1.04-2.63)	0.034	1.88(0.89-3.95)	0.096
50-59	39(17.0)	36(15.7)	1.39(0.83-2.34)	0.214	1.34(0.57-3.12)	0.504
>60	27 (11.7)	13 (5.7)	2.67(1.31-5.41)	0.007	1.49(0.38-5.94)	0.565
Marital status						
Ever Married	207(90.0)	201(87.4)	1:00		NI	
Never married	23(10.0)	29(12.6)	0.77(0.43-1.38)	0.378		
Education level						
Literate	130(56.5)	196(85.2)	1:00	1:00	1:00	
Illiterate	100(43.5)	34(14.8)	4.43(2.83-6.94)	< 0.001	2.57(1.38-4.79)	**0.003**
Occupation						
Employed	70(30.4)	131(57)	1:00	1:00	1:00	
Unemployed	160(69.6)	99(43.0)	3.03(2.06-4.44)	< 0.001	3.78(1.46-9.78)	**0.006**
Income (Birr)	(N=108)	(N=127)				

≥ 2000	52(48.1)	88(69.3)	1:00	1:00	1:00	
<2000	56(51.9)	39(30.7)	2.43(1.43-4.14)	< 0.001	1.76(0.96-3.22)	0.065
BMI(kg/m^2)						
Under weight	30(13.0)	17(7.4)	1:00		1:00	
Normal weight (> 30)	134(58.3))	134(58.3)	0.57(0.29-1.08)	0.083	0.51(0.15-1.72)	0.280
Pre obesity	55(23.9)	55(23.9)	0.57(0.28-1.14)	0.113	0.54(0.15-1.97)	0.347
Obesity	11(4.8)	24(10.4)	0.26(0.10-0.66)	0.004	0.19(0.043-0.826)	**0.027**

Bivariate and multi variable analysis using binary and multivariable logistic regression. 1:00 is Odds Ratio (OR) for reference/comparison group.CI: Confidence interval, COR: Crude Odds Ratio.

5.2.2. Life style risk factors associated with breast cancer

In this study, neither the cases nor the controls had used HRT. Similarly, only three cases, none of the controls were smokers. However, 49 (21.3%) of cases and 66 (28.7%) of controls had a history of alcohol consumption. Concerning dietary habits, significant association was not found between breast cancer with consumption of meat and vegetable. This study also indicated that the odds of breast cancer were 4.04 times (95% CI = 2.67–6.12, P < 0.001) more likely to develop among women who had used solid oil. Similarly, the odds of breast cancer were 6.46 times (3.78–11.03, P < 0.001) higher among women who had used wood or animal dung as a fuel source as compared with women who had used electricity as a fuel source.

Regarding physical activity, women who had strenuous physical activities like running or swimming for less than 5 hours per week had a 0.343 times lower risk of breast cancer (0.343, 95% CI, 0.133–0.887, P = 0.027). Similarly, the odds of breast cancer were 0.228 times lower among women who had a history of moderate physical activity such as walking or playing tennis for less than 5 hours per week. However, after confounding variables were controlled by multivariable logistic regression analysis, consumption of solid oil was significantly associated with breast cancer (AOR, 3.5, 95% CI: 2.18–5.62, p 0.001). Moreover, the odds of breast cancer were 4.91 times higher (95% CI: 2.72–8.86, p< 0.001) among women who used wood or animal dung as a source of fuel compared with women who used electricity. Similarly, the odds of breast cancer were also higher among women who had used a combination of fuel sources

(AOR: 2.57, 95% CI: ,1.56-4.27, P<001). On the other hand, the odds of breast cancer were 0.293 times lower (95% CI: 0.159–0.541, P < 0.001) among women who had moderate physical activities like swimming, table tennis, and basketball for less than 5 hours per week compared with women who had no history of exercise. However, the association between breast cancer and milk intake, fruit intake, alcohol consumption, and frequency of strenuous exercise declined after multiple logistic regression models were applied (Table 10).

Table. 10. Life style risk factors associated with breast cancer at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018-2021,(n=460).

Variables	**Case N (%)**	**Controls N (%)**	**Bivariate analysis**		**Multivariable analysis**	
			COR (95% CI)	**P Value**	**COR (95% CI)**	**P Value**
Alcohol intake						
Non drinker	181(78.7)	164(71.3)	1:00	1:00	1:00	
1glass per week or less	30(13.0)	32(13.9)	0.85(0.49-1.46)	0.554	1.10(0.58-2.09)	0.776
More than 1glass per week	19(8.3)	34(14.8)	0.51(0.28-0.92)	**0.026**	0.66(0.33-1.34)	0.251
Vegetable intake						
More than Once a week	64(27.8)	72(31.3)	1:00			
Once a week or less	166(72.2)	158(68.7)	0.85(0.57-1.26)	0.414	NA	
Fruit intake						
More than Once a week	36(15.7)	20(8.7)	1:00		1:00	
Once a week or less	194(84.3)	210(91.3)	1.95(1.09-3.48)	0.024	0.48(0.22-1.06))	0.070
Meat intake						
More than Once a week	23(10.0)	12(5.2)	1:00		1:00	

Once a week or less	207(90.0)	218(94.8)	2.02(0.98-1.4.16)	0.057	0.93(0.35-2.25)	0.889
Milk take						
More than Once a week	40(15.7)	21(9.2)	1:00		1:00	
Once a week or less	189(82.5)	207(90.8)	2.09(1.19-3.67)	**0.011**	0.47((0.22-1.01)	0.053
Solid oil						
No	45(19.6)	114(49.6)	1:00		1:00	
Yes	185(80.4)	116(50.4)	4.04(2.67-6.12)	**<0.001**	3.50(2.18-5.62)	**<0.001**
Source of fuel						
Electric	54(23.5)	111(48.3)	1:00		1:00	
Wood/Animal dung	88(38.3)	28(12.2)	6.46(3.78-11.03)	**<0.001**	4.91(2.72-8.86)	**<0.001**
Charcoal/Kerosene	3(1.3)	20(8.7)	0.31(0.88-1.08)	0.066	0.26(0.072-0.962)	**0.044**
Combination	85((37.0)	71(30.9)	2.46(1.57-3.87)	**<0.001**	2.57(1.55-4.27)	**<0.001**
Strenuous exercise						
No exercise	209(90.9)	203(88.3)	1:00		1:00	
< 5 Hr. per week	6(2.6)	17(7.4)	0.34(0.13-0.89)	**0.027**	0.58(0.18-1.89)	0.368
5 Hr. and above per week	15(6.5)	10(4.3)	1.46(0.64-3.32)	0.370	1.64(0.58-4.61)	0.351
Moderate exercise						
No exercise	173(75.2)	126(54.8)	1:00		1:00	
< 5Hr per week	21(9.1)	67(29.1)	0.23(0.13-0.39)	<0.001	0.29(0.16-0.54)	<0.001
5 Hr. and above per week	36(15.7)	37(16.1)	0.71(0.42-1.18)	0.188	0.57(0.31-1.06)	0.077

Bivariate and multi variable analysis using binary and multivariable logistic regression. 1:00 is Odds Ratio (OR) for reference/comparison group. Hr: Hour, CI: Confidence Interval, COR: Crude Odds Ratio

5.2.3. Clinical, hormonal and reproductive factors associated with breast cancer

The result of the bivariate analysis of reproductive risk factors revealed that the odds of breast cancer were higher among women who had an age at menarche of less than 12 years (COR: 4.50; 95%: 1.42-14.21, P = 0.010) (Table 11). On the other hand, there was no significant association between abortion or age at first birth and breast cancer. Moreover, the odds of breast cancer were 3.94 times (95% CI = 1.29–12.07, P = 0.016) higher among women who had a family history of breast cancer. Similarly, the odds of breast cancer were 3.94 times higher among postmenopausal women (95% CI: 1.28–12.06, P = 0.016). In addition, women who had previous breast surgery were 5.09 times more likely to develop breast cancer (95% CI: 1.70–15.19, P = 0.04). However, there was no statistically significant association between breast cancer and age at menopause, use of oral contraceptives, duration of breastfeeding, or age at last birth.

Based on the result of multivariable analysis, the odds of breast cancer were higher (AOR, 3.44, 95% CI: 1.80–6.57, p < 0.001) among women who had an age of menarche < 12 years as compared with women > 15 years. Similarly, the odds of breast cancer were also higher among women who had previous surgery as compared with women who did not have a history of previous benign breast surgery (AOR, 7.00, 95% CI: 1.51-32.50, P = 0.013). Moreover, the odds of breast cancer were also higher (AOR, 1.99; 95% CI: 1.20–3.29; P = 0.007) among postmenopausal women compared to premenopausal women (Table 11).

Table 11. Clinical, hormonal and reproductive risk factors associated with breast cancer at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018-2021, (n=460).

Parameter	Case N (%)	Control N (%)	Bivariate analysis		Multivariable analysis	
			COR (95% CI)	P Value	AOR (95% CI)	P Value
Family history of BC						
No	215 (93.5)	226(98.3)	1:00		1:00	
Yes	15(6.5)	4(1.7)	3.94(1.29-12.07)	0.016	2.28(0.60-17.87)	0.169
Age at menarche(years)						
>15	20(11.2)	60(28.6)	1:00		1:00	
12 -15	150(83.8)	144(68.6)	3.13(1.79-5.45)	**<0.001**	6.28(1.73-22.84)	**0.005**
<12	9(5.0)	6(2.9)	4.50(1.42-14.21)	**0.010**	3.44(1.80-6.57)	**<0.001**
Previous benign Breast surgery						
No	211(91.7)	226(98.3)	1:00			
Yes	19(8.3)	4(1.7)	5.09 (1.70-15.19)	**0.004**	7.00(1.51-32.50)	**0.013**
Parity					NA	
Yes	192(83.5)	186(80.9)	1:00			
No	38(16.5)	44(19.1)	0.84(.52-1.35)	0.465		
History of breast feeding					NA	
Yes	186(80.9)	186(80.9)	1:00			
No	44(19.1)	44(19.1)	1.00(0.63-1.59)	1.000		
Duration of BF(n=186)					NA	
37 month and above	126(67.7)	130(69.9)	1:00			

Less than 37 months	60(32.3)	56(30.1)	1.11(0.713-1.72)	0.654		
Age at first birth (yrs.)						
<20	57(33.3)	63(34.8)	1:00		1:00	
20–29	98(57.3)	108(59.7)	1.00(0.64-1.57)	0.990	1.08(0.64-1.81)	0.773
30 and above	16(9.4)	10(5.5)	1.77(0.74-4.21)	0.198	2.02(0.76-5.38)	0.161
Menopausal status						
Premenopausal	117(50.9)	159(69.1)	1:00		1:00	
Post-menopausal	113(49.1)	71(30.9)	2.16(1.48-3.17)	**< 0.001**	1.99(1.20-3.29)	**0.007**
Age at menopause (yrs)					NA	
< 50	65(84.4)	50(79.4)	1:00	1:00		
50 and above	12(15.6)	13(20.6)	0.71(0.29-1.69)	0.439		
Oral contraceptive use						
No	127(55.2)	112(48.7)	1:00		1:00	
Yes	103(44.8)	118(51.3)	0.77(0.534-1.11)	0.162	0.92(0.56-1.51)	0.733
Number of live births					NA	
Greater than 6	20(10.4)	18(9.7)	1:00			
4-6	64(33.3)	58(31.2)	0.99(0.479-2.06)	0.985		
1-3	108(56.2)	110(59.1)	0.88(0.443-1.76)	0.725		
Abortion						
No abortion	163(70.9)	157(68.3)	1:00		1:00	
One	34(14.8)	48(20.9)	0.68(0.42-1.12)	0.127	0.54(0.29-1.01)	0.054
Two and above	33(14.3)	25(10.9)	1.27(0.72-2.24)	0.404	0.96(0.46-1.99)	0.911

5.3. Level of Chemotherapy adherence among breast cancer patents (Paper IV)

5.3.1. Socio demographic Characteristics of study participants

In order to assess the level of adherence for women treated with chemotherapy, a total of 164 breast cancer patients were participated, of which, a total of 119, (72.6%) of the patients were urban dwellers. Moreover, the mean age of the women was 41.99 $\pm$ 10.9 years. Nearly half, 79, (48.2 %) of women were less than 40 years of age. Regarding marital status, the majority 149, (90.9%) of patients were married. Furthermore, more than half 94, (57.3%) of the women were literate. The study also showed, the majority 119, (72.6%) of women were unemployed. Regarding income, more than half 39(52.0%) of women earn a monthly income of less than 2000 Ethiopian Birr per month. The result also showed that, more than half, 91, (55.5%) of women were premenopausal. For the majority, 81, (49.3%) of women, the distance from the referral cancer center was greater than 100 kilometers.

According to the result of Pearson Chi square test, there was no significant difference in the level of adherence based on place of residence and age group of study participants. However, all, 15(100%) of never married women were adherent to their chemotherapy. There was no significant difference in adherence with educational status, employment status, income and menopausal status of women. However, there was significant association between adherence to chemotherapy and distance from the referral cancer center ($P = 0.011$). Patients who come from a long distance had a significantly lower level of adherence (Table 12).

Table 12. Socio-demographic and clinical profile of breast patients on chemotherapy at Tikur Anbessa Specialized hospital, Addis Ababa, Ethiopia, 2018-2021, (n=164)

Variable	Adherent	None adherent	Total (%)	X^2	P- Vlue
	Frequency (%)	Frequency (%)			
Residence					
Urban	102 (85.7)	17(14.3)	119(72.6)		
Rural	35 (77.8)	10(22.2)	45 (27.4)	1.49	0.221
Age group (years)					
Less than 40	65 (82.3)	14(17.7)	79 (48.2)	1.94	0.606
40-49	37 (82.2)	8(17.8)	45 (27.4)		
50-59	17 (81.0)	4(19.0)	21 (12.8)		
60 and above	18 (94.7)	1(5.3)	19 (11.6)		
Marital status					
Ever married	122 (81.9)	27(18.1)	149 (90.9)	3.23	0.135
Never married	15(100)	0(0.0)	15 (9.1)		
Education level					
Illiterate	59 (84.3)	11(15.7.)	70(42.7)	0.050	0.823
Literate	78 (83.0)	16(17.0)	94(57.3)		
Occupation					
Employed	37 (82.2)	8(17.8)	45(27.4)	0.078	0.780
Unemployed	100 (84.0)	19(16.0)	119(72.6)		
Income. Birr (n=75)					
<2000	32(82.1.)	7(17.9)	39(52.0)	0.230	0.632
≥ 2000	31 (86.1)	5(13.9)	36(48.0)		

Menopausal status					
Premenopausal	74 (81.3)	17(18.7)	91(55.5)	0.731	0.392
Post menopauses	63(86.3)	10(13.7)	73(44.5)		
Distance from referral cancer center					
Near the cancer center/100 KM	77(92.8)	6(7.2)	83(50.6)	10.46	**0.015**
100 Km and above	60(74.7)	21(25.92)	81(49.4)		
> 500 KM	16(72.2)	6(27.3)	22(13.4)		

X^2: Chi square, %: Percent

5.3. 2. Distribution of personal characteristics of study participants

In this study 11, (6.7%) of patients had a family history of breast cancer. Even though there was no significant association, level of adherence was higher among patients with a family history of breast cancer. Regarding smoking, only, 3 (1.8%) of patients had a history of smoking cigarettes. However, 28, (17.1%) of women had a history of drinking alcohol. Moreover, almost one fourth, 39, (23.8 %) of the study participants had experience of moderate exercise. On the other hand only, 12 (7.3%) of women had experience of strenuous exercise before they had been diagnosed with breast cancer. Among a total of 39 women who had experience of moderate physical exercise, the majority, 35(89.7%) of women adhere to their chemotherapy as compared with only 4(10.3) women who did not adhere to their chemotherapy. In general there was no statistically significant difference between adherence to chemotherapy with family history, cigarette smoking, alcohol consumption and physical activity. In general, based on the result of chi-square test there was no significant association between different personal/ life style factor and level of adherence for chemotherapy (Table 13).

Table 13. Personal characteristics and level of adherence among breast patients on chemotherapy at Tikur Anbessa Specialized hospital, Addis Ababa Ethiopia, 2018-2021 (n=164)

Variable	Adherent F(%)	None adherent F(%)	Total	X^2	P- Value
Family history of breast cancer					
No	127(83.0)	26(17.0)	153(93.3)	0.466	0.495
Yes	10(90.9)	1(9.1)	11(6.7)		
Smoking Cigarettes					
No	134(83.2)	27(16.8)	161(98.2)	0.602	0.438
Yes	3(100)	0(0.0)	3(1.8)		
Alcohol intake					
No	113(83.1)	23(16.9)	136(82.9)	0.116	0.733
Yes	24(85.7)	4(14.3)	28(17.1)		
Moderate exercise					
No	102(81.6)	23(18.4)	125(76.2)	1.43	0.231
Yes	35(89.7)	4(10.3)	39(23.8)		
Strenuous exercise					
No	126(82.9)	26(17.1)	152(92.7)	0.622	0.430
Yes	11(91.7)	1(8.3)	12(7.3)		

X^2: Chi square, F: Frequency, %: Percent

5.3.3. Clinical characteristics of study participants

In this study, 12, (7.3%) of women underwent previous breast surgery, and the adherence level was almost the same between women who underwent previous breast surgery and those who did not undergo surgery. The finding also showed that the majority, 73, (44.5%) of women had stage III tumor at diagnosis. Similarly, the commonest pathological diagnosis among the patients was invasive ductal carcinoma, 144, (87.8%). In general there was no statistically significant association between level of adherence with different stages of tumors and pathological diagnosis. This study also found that, more than half, 104 (63.44%) of patients were planned for eight courses of chemotherapy, while 52, (31.7%) and 8, (4.9%) of patients were planned for six and four courses regimens of chemotherapy, respectively. Based on the Pearson chi-square test, there was a significant difference between the level of adherence and recommended chemotherapy regimen (Table 14).

Table 14. Clinical characteristics and level of adherence among breast cancer patients attended chemotherapy at Tikur Anbessa Specialized hospital, Addis Ababa Ethiopia, 2020.

Variable	**Adherent Frequency (%)**	**None Adherent Frequency (%)**	**Total Frequency (%)**	**X^2**	**P- Value**
Patient with previous breast surgery					
No	127(83.6)	25(16.4)	152(92.7)	0.001	0.984
Yes	10(83.3)	2(16.7)	12(7.3)		
Stage at diagnosis					
I&II	35(79.5)	9(20.5)	44(26.8)	5.52	0.124
III	63(86.3)	10(13.7)	73(44.5)		
IV	39(83.3)	8(17.0)	47(28.7)		
Histology type					

Ductal	121 (84.0)	23(16.0)	144(87.8)	0.796	`0.850
Lobular	6(85.7)	1(14.3)_	7(4.3)		
Mixed	5(83.3)	1(16.7)	6(3.7)		
Other/unspecified	5(71.4)	2(28.6)	7(4.3)		
Course of recommended therapy					
Eight	93(89.4)	11(10.6)	104(63.4)	8.50	**0.014**
Six	37(71.2)	15(28.8)	52(31.7)		
Four	7(87.5)	1(12.5)	8(4.9)		

X^2: Chi square, %: Percent

5.3.4. Reasons for non-adherence to chemotherapy

In this study, for chemotherapy non-adherence, the reason was unknown for 7, (25.9%) of women. Even though, different reasons were identified for non-adherence, pain or severity of disease was most frequently encountered reason for non-adherence among 9 (33.3%) of the patients. In addition, financial constraints 4, (14.8%), and security or distance from cancer referral center, 3 (11.1%) were also identified as factors for non-adherence. In addition, pregnancy, comorbidity, feeling well, use of traditional medicine was also contributed for non-adherence for chemotherapy (3.7% for each).

5.4. Survival analysis of breast cancer patients (Paper V)

5.4.1. Socio demographic characteristics of breast cancer patients

In order to assess survival of breast cancer patients, a total of 402 patients were identified from patient's charts. The median follow up was 58.26 months. The majority of patients, 203 (50.5%) were from Addis Ababa. Concerning age, more than one third, 109, (39.8%) of patients were less than 40 years old. The median age was 43.4[35-50] years. At the end of follow-up, 169, (42%) patients were alive (censored) and 233, (58%) patients were dead (Table 15).

Table15. Socio demographic characteristics of breast cancer patients attended treatment at Tikur Anbesa Specialized Hospital, 2018-2021, (N=402).

Variables	**Patient status**		**Total N (%)**
	Censored N (%)	**Death N (%)**	
Residence			
Addis Ababa	91 (44.8)	112 (55.2)	203(50.5)
Oromia	38 (38.0)	62 (62.0)	100 (24.9))
Amhara	15(31.9)	32 (68.1)	47 (11.7)
SNNP	9(34.6)	17(65.4)	26 (6.5)
Tigray	6(42.9)	8 (57.1)	14(3.5)
Other	7(87.5)	1 (12.5)	8(3.0)
Age at diagnosis			
Less than 40	64 (40.3)	95(59.7)	159(39.8)
40-49	45 (41.3)	64(58.7)	109 (27.3)
50-59	43 (47.3)	48(52.7)	91(22.6)
60 and above	17(37.5)	26(62.5)	40(10.0)
Median age at diagnosis: 43.4[35-50] years			

5.4.2. Clinical and tumor related characteristics of Breast Cancer patients

Almost half, 200 (49.8%) of study participants had a left side tumor. Two hundred six patients (51.2%) were in stage III, followed by 100 (24.9%) in stage IV. However, very few, 11 (2.7%) of the patients were in stage I; of the total stage IV patients, the majority, 83, (84.7%) of them died (Figure 4).

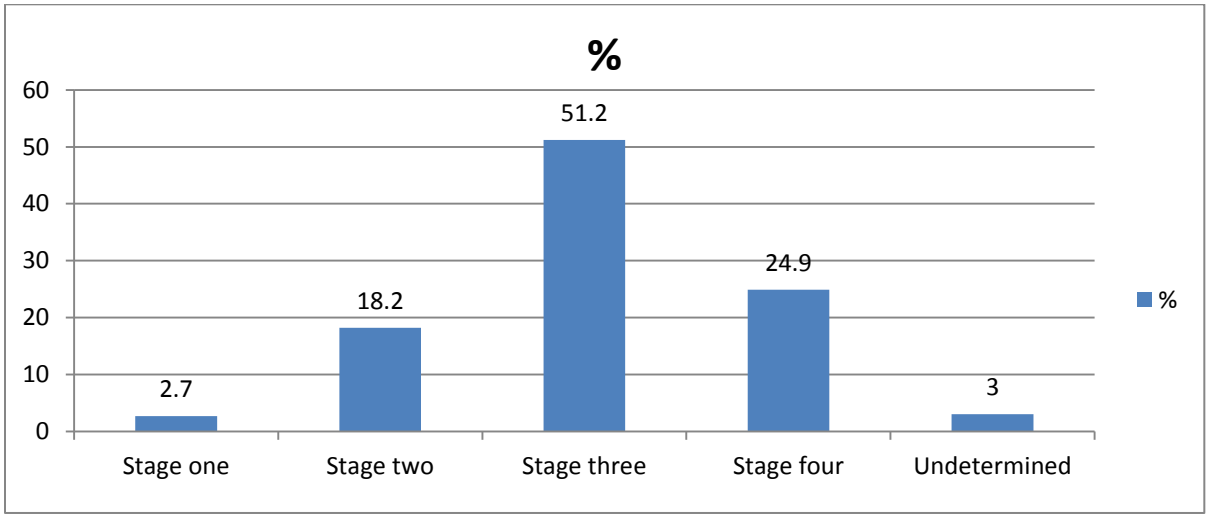


Figure 4. Distribution of patients according to stage of tumor at diagnosis at Tikur Anbesa Specialized Hospital (N=402)

In this study nearly half, 200 (49.8 %) of the study participants were treated with left side tumor. Similarly, majority, 206, (51.2%) of the study participants were with stage III tumor at time of diagnosis. This study also found that, the majority, 332(82.6) of patients were diagnosed with ductal carcinoma with undifferentiated tumor grade being detected in 139(34.6) patients. Besides, 111 (27.6) of study participants had metastasis to distal organs at diagnosis, of which 42 (37.8) had lung metastasis. Overall, among patients with metastasis tumors, the majority, 94, (84.71%) of them died. The mean tumor size was 4.92 $\pm$ 4.22 cm. Majority of study participants 131, (32.6%) had tumor size greater than 5 cm, of which 90, (68.7%) had died. Primary treatment was surgery in 317, (78.9%) of patients, followed by chemotherapy, 69, (17.2%). In general, 362, (90.5%), 185(46.0%) of patients were treated with chemotherapy and hormone therapy, respectively. However, 23, 5.7% of the study participants had unknown status for chemotherapy, of which, majority, 21, (91.3%) of them were dead (Table 16).

Table 16. Clinical and tumor-related characteristics of breast cancer patients attending treatment at Tikur Anbesa Specialized Hospital, 2018-2021 (n=402).

Variables	Patient status		Total N (%)
	Censored N (%)	Death N (%)	
Tumor side			
Right	69(37.5)	115(62.5)	184(45.8)
Left	93(46.5)	107(53.5)	200(49.8)
Bilateral	1(14.3)	6(85.7)	7(1.7)
Unknown	6(54.5)	5(45.5)	11(2.7)
Stage			
I	9(81.8)	2(18.2)	11 (2.7)
II	55(75.3)	18(24.7)	73(18.2)
III	86(41.7)	120(58.3)	206(51.2)
IV	15(15.3)	83(84.7)	98(24.3)
Unknown	4(28.6)	10(71.4)	14(3.5)
Histology			
Ductal	137(41.3)	195(58.7)	332(82.6)
Lobular	11(57.9)	8(42.1)	19(4.7)
Other/unspecified	21(41.2)	30(58.8)	51(12.7)
Grade			
Grade I	37(63.8)	21(36.2)	58(14.4)
Grade II	54(49.4)	83(60.6)	137(34.1)
Grade III	28(41.2)	40(58.8)	68(16.9)
Undifferentiated	50(36.0)	89(64.0)	139(34.6)
Recurrence (n=394)			
No	142 (44.4)	178 (55.6)	320(81.2)
Yes	24 (32.4)	50 (67.6)	74 (18.8)
Metastasis to distal organ			
No	152(52.2)	139(47.8)	291(72.4)
Yes	17(15.3)	94(84.71)	111(27.6)
Tumor size (cm)			
< 2	5 (3.7)	6 (3.3)	11(3.5)
2-5	89(65.9)	85(47.2)	174 (55.2)
> 5	41 (30.4)	89 (49.4)	130 (41.3)
Mean tumor size: 4.92 $\pm$ 4.22 cm			
Primary treatment			
Surgery	153(48.3)	164(51.7)	317 (78.9)
Chemotherapy	15(21.7)	54 (78.3)	69 (17.2)
Other	1 (6.3)	15(93.7)	16 (4.0)
Chemotherapy			
Yes	158 (43.6)	204 (56.4)	362(90.5)
No	9 (52.9)	8 (47.1)	17 (4.3)
Unknown	2 (8,7)	21(91.3)	23(5.7)

Hormone			
Yes	92(49.7)	93(50.3)	185(46.0)
No	41(37.6)	68(62.4)	109(27.1)
Unknown	36(33.3)	72(66.7)	108(26.8)
Radiation			
Yes	70(54.7)	58(45.3)	128(31.8)
No	46(33.3)	92(66.7)	138(34.3)
Unknown	53(39.0)	83(61.0)	136(33.8)

5.4.3. Survival status of breast cancer patients

This study also revealed that the median follow up time was 52.8 months. Using Kaplan Meier analysis the overall median survival time was 61.96 (95% CI: 49.71-74.41) months. There was no significant difference in median survival of patients residing in or outside Addis Ababa (63.90, 95% CI, 45.25-82.54 and 55.50, 95% CI: 43.10 to 67.89), P= 0.431). Similarly, there was no significant difference in median survival of patients with recurrence status, histology type, and age at diagnosis. The one, two, and three year survival rates were 85%, 75%, and 62%, respectively. Whereas the five and ten year survival rates were 50% and 34% respectively. Based on the result of Kaplan Meier analysis there was a highly significant survival difference among women based on stages of disease. As compared to stage I, stage IV patients have a lower chance of survival, with median survival of 21.80 (95% CI 13.75-29.84, P = 0.001) months (figure 5). Women who had poorly differentiated or undifferentiated nuclear grade tumors have also significantly lower chances of survival. Compared to patients with tumor size less than 2cm, patients with tumor size greater than 5 cm had significantly poor median survival (43.73, 95% CI, 32.11-55.35, P < 0.001). Better median survival, 81.80(66.15-97.45, P < 0.001)) months, had seen among patients who were primarily treated with surgery because patients treated primarily are in the early stage and receive additional therapy as well- chemo, radio, or hormone therapy. Significantly low median survival was also recorded in patients who received neither chemotherapy nor radiotherapy (Table 17).

Table 17. Median survival time and log rank tests based on different characteristics of breast cancer patients on treatment at Tikur Anbesa Specialized Hospital, 2018-2021 (n=402).

Variable	Median survival time in months (95% CI)	Log rank test
Place of residence		
Addis Ababa	63.90(45.25-82.55)	0.431
Outside Addis Ababa	55.50(43.10- 67.89)	
Age (years)		
Less than 40	55.50(41.71-69.28)	0.764
40-59	66.90(50,14--83.66)	
60 and above	57.23(44.68-69.78)	
Recurrence		
No	66.90(50.63-83.16)	0.063
Yes	49.60(38.16-61.03)	
Tumor size (Cm)		
Less than 2	79.67(37.55121.77)	**0.001**
2-5	92.50(75.05-19.94)	
Greater than 5	43.73(32.11-55.35))	
Primary treatment		
Surgery	81.98(66.15-97.45)	**0.001**
Chemotherapy	25.73(18.19-33.21)	
Other	11.00(3.22-18.77)	

5.4.5. Kaplan-Meier Survival analysis

Based on the result of Kaplan-Meier Survival analysis, median survival and survival probability was calculated. The result showed that for stage IV patient's median survival time was 21.80 (95% CI 13.75-29.84) months. Which was significantly lower (P < 0.001) as compared to patients with stage I and II. It is known that patients diagnosed at an advanced stage have worse survival (Figure 5).

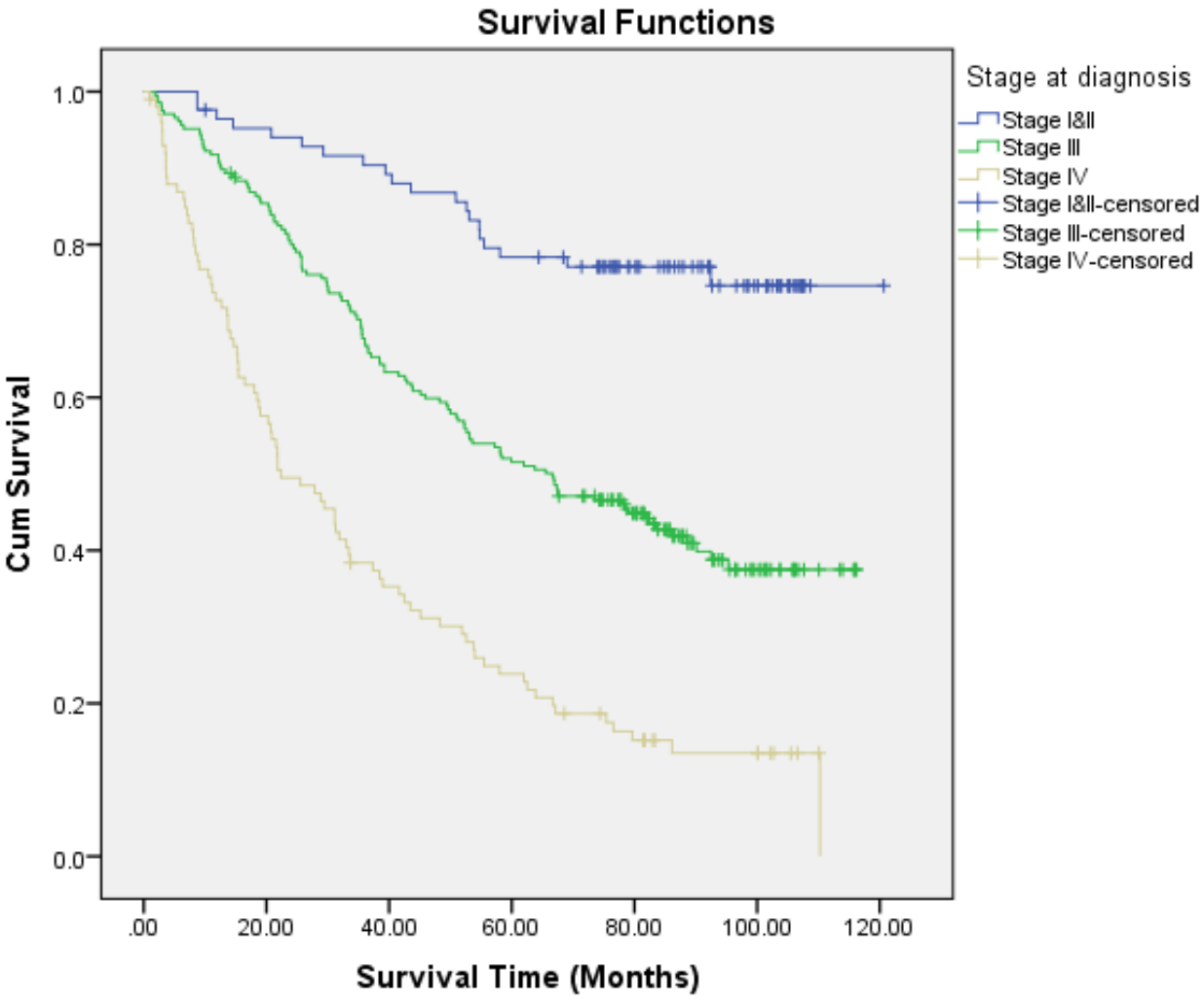


Figure 5. Stage at diagnosis and overall survival rate of breast cancer patient's treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018-2021, (n=402).

On the other hand, the finding also showed that , based on the result of Kaplan-Meier Survival analysis, there was significantly better median survival, 81.80, 95% CI, (66.15-97.45),) months, among patients who had been primarily treated with surgery. Log rank, P <0.001 as compared to other forms of treatment (Figure 6).

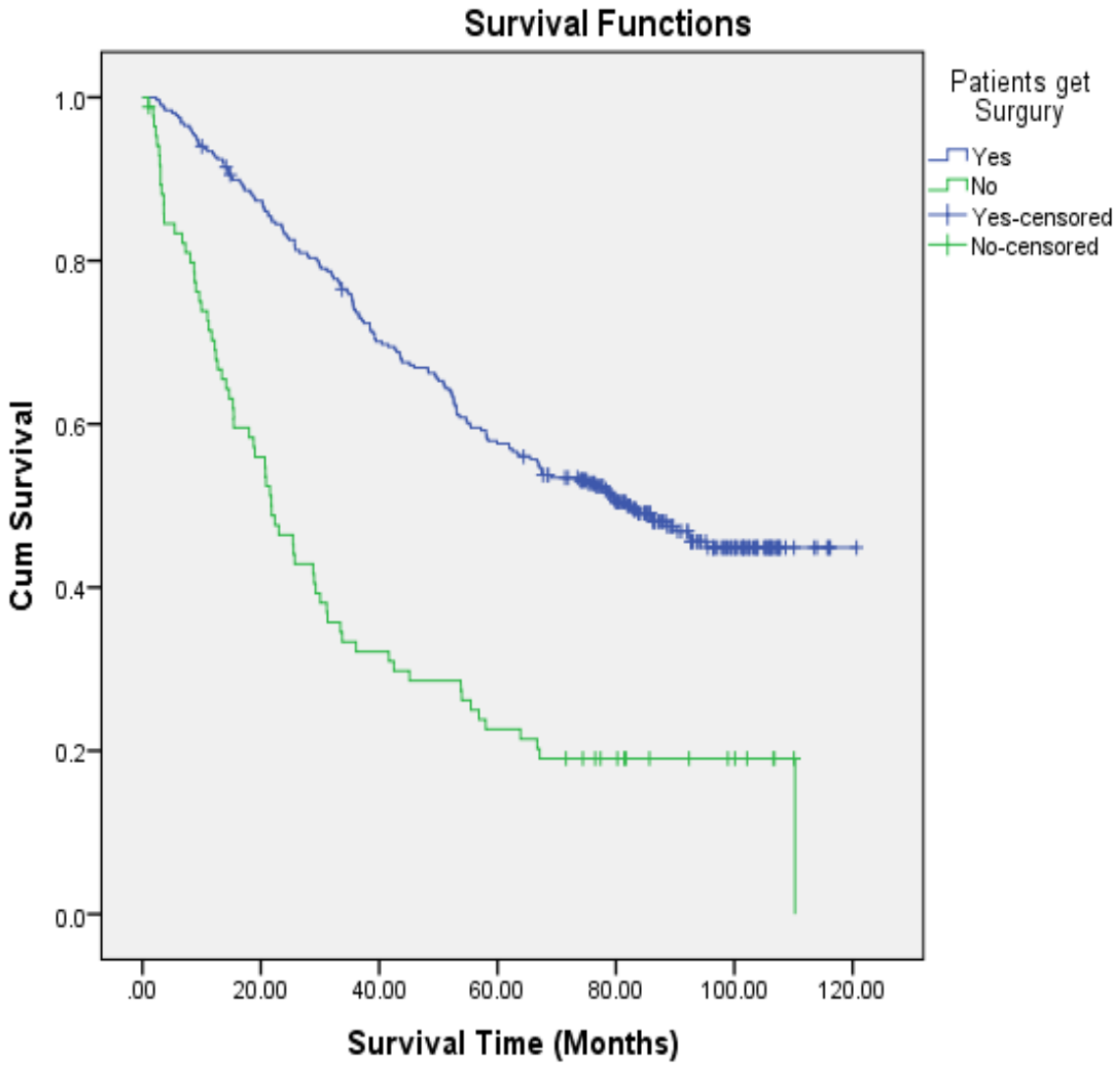


Figure 6. Overall survival rate of breast cancer patients who had got surgery as primary treatment at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2018-2021, (n=402).

As indicated in the above section, 27.6 % of women had metastasized tumor. Based on the result of Kaplan-Meier Survival analysis, compared to patients without metastasized tumor, patients with metastasized tumor had significantly lower median survival 29.43 95% CI (19.85-39.0) months, log rank, P <0.001) (Figure 7).

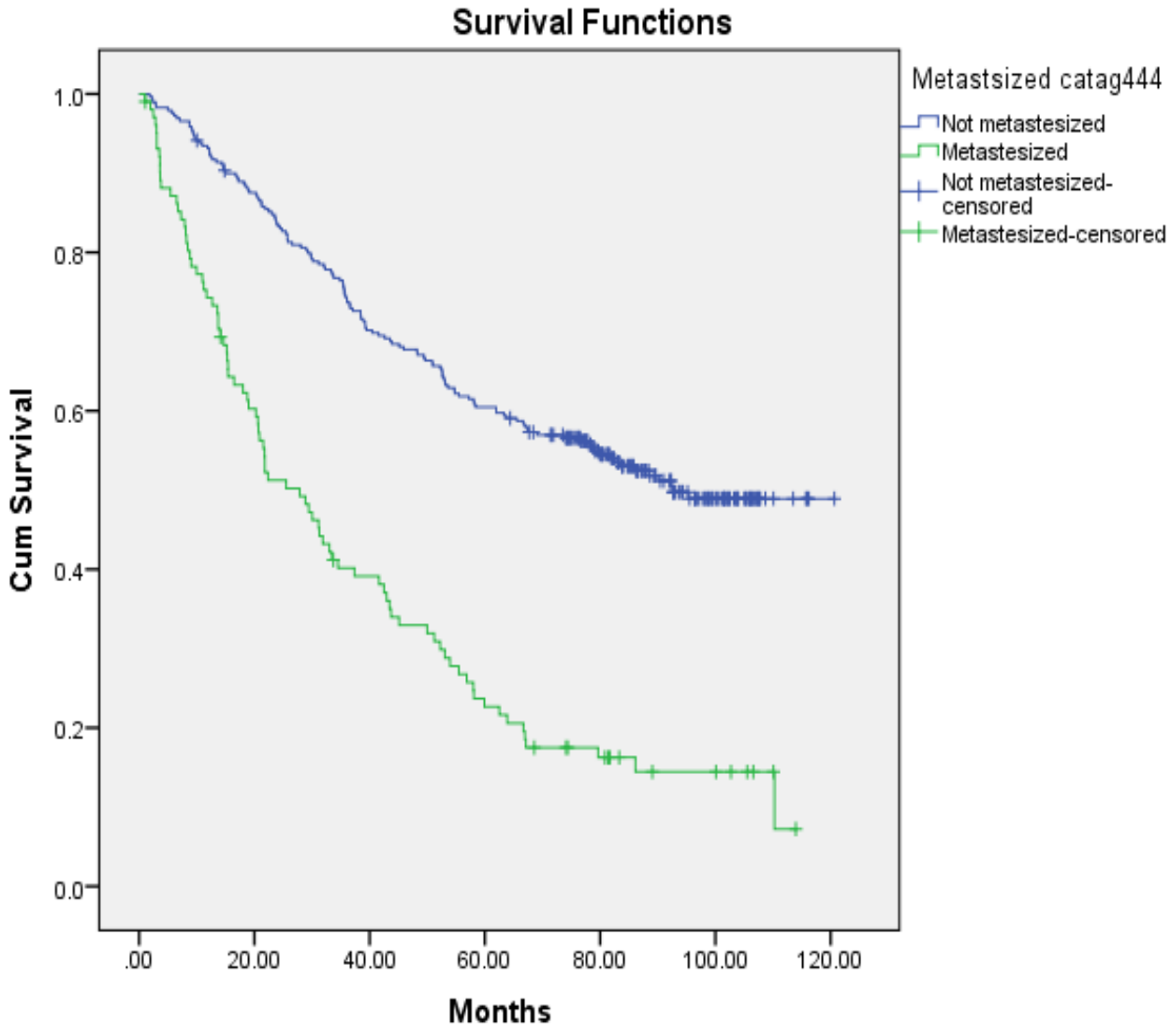


Figure7. Metastasis status and overall survival rate of breast cancer patients treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

5.4.6. Bivariate and multivariable cox regression analysis

According to bivariate cox regression analysis there was no significant difference in survival of patients by age groups, types of tumor histology and tumor size (P >0.05) (Table 18). However, being in stage four had 7.65 times higher risk of death with HR= 7.65 (4.68-12.51, P< 0.001) compared to patients with stage one. Patients with higher grade (grade III) or undifferentiated tumor had also higher risk of death as compared to those with lower grade tumor (grade I). Moreover, patients with grade III/un differentiated tumors had 2.23 times higher risk of death (HR=2.23; 95% CI: 1.41-3.54, P < 0.001). Besides, there was significant difference in survival by tumor metastasis status of patients at time of diagnosis with crude HR, 2.02, 95%(1.63-2.55, P<0.001). According to type of treatment, patients who were not treated with surgery had significantly worse survival with crude (HR=2.85, 95% CI (2.15- 3.79).

Based on multivariate cox regression analysis, stage at diagnosis, metastasis status and treatment status of patients remained significantly associated with worse survival. Patients with stage four tumors had 5.39 times higher death hazard as compared to women with stage one and stage two (HR=5.39; 95% CI: 2.43-11.93, P< 0.001). Moreover, patients with metastasized tumors had a 1.78 times higher death hazard as compared to those women without metastasized tumors (1.78; 95% CI: 1.10- 2.47, P = 0.044). However, after adjusting for confounding variables, the protective role of surgery as treatment did not reach statistical significance (HR; 1.47; 95% CI: 0.85-2.54, P=0.166). On the other hand, compared to those women who were treated with hormone therapy, women who were not treated with hormone had 1.65 times higher death hazard (HR; 1.65; 95% CI, 1.10-2.47, P = 0.015). There is weak evidence to suggest women who were not treated with radiation had higher death hazard compared to women with radiation therapy (HR; 1.50; 95% CI: 0.961-2.36, P = 0.074) (Table 18).

Table 18. Bivariate and multivariable analysis of different variables with survival time for breast cancer patients on treatment at Tikur Anbesa Specialized Hospital, 2018-2021, (n=402)

Factors	**Censored**	**Death**	**Univariate cox regression**		**Multivariate cox regression**	
	N	**%**	**HR† (95% CI)**	**P value**	**HR∗(95%CI)**	**P value**
Place of resident					NI	
AA	91(44.8)	112(55.2)	1:00			
Outside AA	78(39.2)	121(60.8)	1.11, (857-1.43)	0.432		
Age at diagnosis					NI	
Less than 40 years	64(37.9)	95(40.8)	1:00			
40-59 years	88(52.1)	112(48.1)	0.91(0.69-1.19)	0.477		
Greater than 60 years	17(10.1)	26(11.2)	0.98(0.64-1.52)	0.941		
New or recurrence						
No	142(85.5)	178(78.1)	1:00			
Yes	24(14.5)	50(21.9)	1.35(0.98-1.84)	0.065		
Stage at diagnosis						
I &II	64(38.8)	20(9.0)	1:00		1:00	
III	86(52.1)	120(53.8)	3.17 (1.97-5.08)	0.001	5.39(2.43-11.93)	**0.001**
IV	15(9.1)	83(37.2)	7.65(4.68-12.51)	0.001	5.53(2.09-14.61)	**0.001**
Tumor size(n=315)					NI	
<2cm	5(3.7)	6(3.3)	1:00			
2-5 cm	89(65.9)	85(47.2)	0.89(0.39-2.05)	0.794	NI	
>5cm	41(30.4)	89(49.4)	1.56(0.68-3.57)	0.293		
Nuclear grade						
Grade I	37(21.9)	21(9.0)	1:00		1:00	
Grade II	54(32.0)	83(36.5)	2.06(1.27-3.32)	0.003	2.44(1.08-5.52)	**0.032**
Grade III/Undiff.	78(46.2)	129(55.4)	2.23(1.41-3.54)	0.001	1.87(0.84-4.17)	0.127
Pathology					NI	
Ductal	137(81.1)	195(83.7)	1:00			
Lobular	11(6.5)	8(3.4)	0.676(0.333-1.37)	0.279		

Other /unspecified	21(12.4)	30(12.9)	1.06(0.719-1.55)	0.779		
Metastasis status						
No	152(89.9)	139(59.7)	1.00		1:00	
Yes	17(10.1)	94(40.3)	2.04(1.63-2.55)	0.0001	1.78(1.10-2.47)	**0.044**
Surgery						
Yes	317	78.9	1:00		1:00	
No	85	21.1	2.85(2.15- 3.79)	0.001	1.47(0.852-2.54)	0.166
Chemotherapy						
Yes	158	204	1:00		NI	
No	9	8	0.82(0.40-1.66)	0.578		
Hormone						
Yes	185	62.9	1:00		1:00	
No	109	37.1	1.48(1.08-2.02)	0.041	1.65(1.10-2.47)	0.015
Radiation						
Yes	128	48.1	1:00		1:00	
No	138	51.9	2.04(1.47-2.83)	0.001	1.50(0.961-2.36)	0.074

†Unadjusted Hazard Ratio; ∗Adjusted Hazard Ratio, NI= not include, AA: Addis = Addis Ababa

6. Discussion

6.1. Sociodemographic and hematologic profile of breast cancer patients (Paper I)

Both developed and developing nations struggle with the serious public health issue of breast cancer since its incidence is rapidly increasing [4]. Different sociodemographic and hematologic characterizations are very important and should be considered in order to maximize treatment success and patient survival. This study revealed that the bulk of breast cancer cases come from Addis Ababa City, followed by the Oromia region, which could be because Addis Ababa is a place where the referral cancer center is found. Moreover, since the Oromia region surrounds Addis Ababa city, most patients from the nearby Oromia region might have easier access due to the proximity as compared to other regions, which are very far from the cancer referral center. Moreover, the majority of patients were also urban dwellers. Regarding age majority (54.3%) of the study participants were less than 40 years of age. This finding is comparable with different studies conducted in Ethiopia [128, 23, and 129].

This indicated that younger women are more susceptible or highly affected, unlike women in developed countries. However, our finding is not in line with a study done in Iraq [62]. This difference could be due to diet, lifestyle, genetics, population characteristics, and other related factors. Even though breast cancer incidence is supposed to be higher in people above 50 years of age, in this study, 15.2% of cases were found to be below 30 years old, which is in line with another study done in Ethiopia [129]. Overall, this study revealed that the majority, 76.5% of breast cancer patients were younger than 50 years old. This finding is somehow comparable with a study done in Pakistan, Sindh [130]. Moreover, there was no significant difference in breast cancer based on residence.

Regarding educational status, the majority, 100 (43.5%) of cases and 34 (14.8%) of controls, were illiterate. This finding is in agreement with different studies done in India [47,48]. On the other hand, this study was not supported by a similar study done in Mozambique, which indicated that higher educational levels increase breast cancer risk [53]. This discrepancy could be due to their lifestyle, including their feeding habits or physical activity, a smaller sample size, or the study setting. It might also be due to the definition of educated women in the Mozambique study, where higher educational status is defined as $\geq$ 8 schooling years, which is different from

our definition. In general, a significant number (34.3%) of cases, as compared to 12.6% of the controls, had a monthly income of less than 2000 Ethiopian birr. This finding was supported by a similar study done in Babylon Province, which showed that low economic status was significantly associated with breast cancer [52]. However, based on another study, the distribution of cancer was known to be more prevalent in socioeconomically better individuals, presumably owing to the lifestyle risks they are exposed to [131]. The majority (76.1% of the cases) were married. That seems to be equivalent to a study done in Ethiopia [25].

There was a significant association between breast cancer and women being illiterate, having a lower income, and being housewives. This finding was supported by a similar study done in Bangui, Central African Republic, which reported that women with breast cancer were more likely to be illiterate or have primary education, and being employed was protective for breast cancer compared to being a housewife [132]. On the other hand, there was no significant association between place of residence, age, or marital status and breast cancer. However, this finding was not supported by a similar study in Bangui, which reported that breast cancer was significantly higher among married women [132]. This difference could be due to differences in sample size and study setting. Regarding age, even though a study found that breast cancer risk is increasing with age [133], the majority of breast cancer patients in this study were less than 50 years of age. This finding was supported by similar studies done in Ethiopia [20,113, 134].

Even though our control was hospital controls, since they are healthy, it might not cause under or over estimate of risks. In addition, most of potential risk factors might be similar among cases and controls. In light of this, it's possible that our hospital controls might have no difference or little differences from general population controls for most exposure variables. The controls, however, were more educated and younger since younger people with higher levels of education are typically chosen to be caregivers. This circumstance could lead to an overestimation of participants' educational attainment and an underestimation of their age.

This study found that the mean values of hemoglobin, RBCs, and PCV were significantly lower among cases compared to healthy controls. This finding is comparable with different studies from Iraq, Sindh, Nigeria, and Algeria [65-68]. Since HB and PCV are used as guides to diagnose anemia, and anemia is one of the major problems for most cancer patients, those

parameters are usually lower compared to healthy controls [65, 66, 130]. This low level of hematological parameters may be associated with bone marrow or immune suppression as a result of the cancer itself. The other possible reason could be that if the patient's condition were pre- or post-surgery, these parameters could be significantly reduced. In addition, the nutritional status and clinical conditions of patients could also play an important role in the reduction of such values.

We found that the mean platelet count was significantly increased among cases as compared with controls. This finding is not comparable with a study done in Sri Devaraj Urs Medical College, Tamaka, Kolar, Karnataka, which revealed that even though platelet count is higher among cases, the difference was not significant [66]. This difference could be due to the fact that the majority of cases were stage II tumors, and the numbers of controls were only 20 participants with benign breast disease, which might have implications since platelet count increases with the advanced stage of the disease. However, in our study, this higher platelet count might be associated with the advanced stage of breast cancer patients, since higher platelet levels are associated with poor prognosis and survival [135].

In this study, there was no significant difference in total WBC count between cases and controls, which was comparable with a similar study done in India [65]. However, our finding is lower than a previous study done in Nigeria, which found that the total WBC count of breast cancer cases were significantly lower [67]. This difference could be due to the fact that breast cancer cases were at different stages of therapy, unlike our study participants, who were newly diagnosed breast cancer patients. In this case, being on different forms of therapy might affect total WBC count, and this parameter will be significantly affected.

Our study found that anemia was prevalent in 20.4% of cases and 5.6% of controls, which is comparable with a similar study conducted in Ethiopia [136]. This study also indicated that leukopenia was found in 5.7% of cases and 3.9% of controls, which is nearly comparable with a study done in India [65]. Thrombocytosis was observed in 23.5% of the cases and 7.8% of the controls.

6.2. ABO/Rh Blood group profile of breast cancer patients (Paper II)

Our study aimed to assess the association between ABO-Rh type and breast cancer by studying 191 cases and 230 healthy controls. The findings showed that blood group O was the predominant and group AB was the least frequent among breast cancer patients as well as healthy controls. In general, the distribution of the ABO blood group was O> A >B > AB, which was comparable with a study conducted in Tanzania, which reported that the O blood group was (52.3%) and the least common was the AB blood group (3.18%) [137]. Regardless of breast cancer status, the findings of this study was also comparable with studies done in different parts of Ethiopia, like Arbaminch, which found that the majority (41.20%) had blood type 'O' , [138], Gambella, 41.2% group O and 3.34 group AB [139], and Debre Tabor, 39.6% O and 7% AB [140]. However, these frequencies have certain variations among different ethnic groups and geographical locations. For example, as indicated in the previous study from Gambella, blood group A was the predominant (44.07%) blood group among highlanders, whereas blood group O was the most frequent (50.42%) blood group among Nilotic natives [139].

It was also found that 7.1% of the study participants were Rh-negative. This finding is comparable with other studies in Ethiopia that reported 7-8% Rh negativity [138-140], which is also consistent with our finding. On the other hand, a lower frequency of Rh-blood type was reported from Tanzania (2.3%) [137]. A study from China found that ABO and Rh blood distributions were significantly different among nine ethnic groups [141]. The issue of ethnic differences has also been reinforced by a study from Gambella, west Ethiopia [139]. The study found that 19.37% of study participants were Rh-negative, a frequency that is much higher than previous studies conducted in different parts of Ethiopia [139].

Numerous diseases, including breast cancer, have been linked to specific blood types. Although findings are inconsistent and unclear, there have been several studies conducted on the association between blood groups and the risk of breast cancer [81-84]. However, in the current study, there was no significant association between ABO blood types and breast cancer incidence. This difference could be due to genetic differences in the study population, which might have the variability of minor alleles in different study populations.

There are studies that found that the risk of breast cancer is significantly higher among women who have blood group A, and there is a minimum risk among women with blood group AB [78–81,84]. On the other hand, a study from Iraq showed that the O+ blood group was associated with the risk of breast cancer [85]. This study also found that Rh type had no significant association with the risk of breast cancer. This finding is supported by a similar study done in India [87].

6.3. Risk factors associated with breast cancer (Paper III)

We found that potential risk factors associated with breast cancer were examined. The present study found that, as shown by previous studies [142,143], a variety of risk variables, including demographic, lifestyle, reproductive, and hormonal factors, contributed to the incidence of breast cancer. Environmental factors may have direct effects, or they may act indirectly through mediators such as obesity or earlier puberty. Since, we are clearly in an era when complex interactions, upstream causal factors, and multiple pathways of causation must be considered [144].

Our study revealed that there were no women who had taken HRT, and there was also no conclusive link between breast cancer and oral contraceptive use, alcohol consumption and smoking. However, a review of environmental factors found that the use of hormone therapy, which combines estrogen and progestin, exposure to ionizing radiation, excess weight in post-menopausal women, eating unhealthily, drinking alcohol, and exposure to these factors all increased the risk of breast cancer [145, 146]. Furthermore, research on a number of substances has shown that early-life exposure to environmental variables increases the risk of developing breast cancer [147].

In our study, there was no correlation between breast cancer risk and reproductive caracterstics as age at menopause, parity abortion and breast feeding status of women. However, a study revealed that environmental or reproductive factors that have changed over time may contribute for the rise in breast cancer incidence. Reproductive patterns vary as fertility rates fall in developing nations. Women may start having children later in life, finish having children sooner

in life, and modify how far apart their pregnancies are from one another. In addition to the obvious advantages of having fewer kids, these timing and spacing modifications are [148].

Our findings indicate that there was no meaningful relationship between breast cancer and the study participants' marital status or place of residence. According to bivariate analysis, although women between the ages of 40 to 49 and women > 60 years of age had a greater chance of developing breast cancer, however this link declined when the multivariable regression model was used. Thus, there was no significant difference in odds or the magnitude of breast cancer among young and older women. On the other hand, illiterate women had higher odds of breast cancer than literate women (AOR, 2.57 95% (1.38–4.79), P = 0.003). This conclusion is supported by a related study conducted in Bangui that found that illiterates had greater odds of breast cancer [132]. The odds of breast cancer were also higher among unemployed women compared with employed women (AOR, 3.78; 95% CI, 1.46–9.78). That finding was also supported by a previous study done in Bangui [132]. The current study, however, could not be compared to a study from India that found that women with greater educational status were more likely to get cancer of the breast [143]. This difference could be due to the fact that education might affect women's exposure to modifiable breast cancer modifiable risk factors, including socioeconomic status, lifestyle, reproductive, and behavioral factors. These factors could be explained by consumption of processed food, inactivity or sedentary life, limited parity, delayed age at first birth, short duration of breastfeeding, and exposure to HRT, which may contribute to a high risk for breast cancer.

Despite the fact that BMI has been linked to an elevated risk of breast cancer in the past [149], the BMI of cases in this study was lower than that of controls. This lower BMI among cases may be the result of cases losing weight as a result of their illness. This result is equivalent to that of the Malaysian study [150]. However, another study found that postmenopausal women with normal BMIs and relatively high body fat levels had an increased risk of developing invasive breast cancer. The study also explained that normal BMI categorization may not be a reliable proxy for the risk of breast cancer in postmenopausal women [151]. Alcohol consumption, meat consumption, or vegetable consumption were not found to be significantly correlated with breast cancer in this study. A similar study carried out in the US, however, found that a higher intake of

fruits and vegetables was linked to a lower risk of breast cancer [152], which contradicts this finding. This difference could be due to the difference in type and dosage pattern of such fruit- and plant-based dietary patterns. The other possible explanation could be that consumption of such diets may be limited among study participants due to limited buying capacity.

According to bivariate analysis, women who drank milk once a week or less had 2.08 times higher odds of breast cancer than those who drank it more frequently. However, that association declined after the multivariable logistic regression model was applied. Our results are not comparable to those of other studies, which showed an inverse relationship between dairy consumption and the risk of breast cancer [153,154]. This variation may result from the dosage, type of dairy, and timing of the consumption of such products. Additionally, we discovered that the likelihood of breast cancer was 3.50 times higher in women who used solid oil at room temperature compared to women who did not, since saturated fat consumption raises the risk of breast cancer. An American study [155] that was conducted backed up this conclusion. Furthermore, this study also supported by study done in ….which indicated that early exposure to environmental carcinogens, endocrine disruptors, and unhealthy foods like refined sugar, processed fats, food additives are hypothesized to promote molecular damage that increases breast cancer risk [146].

Our study also revealed that women who used wood or animal dung as a fuel source had 5.91-times higher odds of developing breast cancer, which was supported by another study done in the USA [156]. This might be due to the fact that burning biomass, such as wood, in the home can result in exposure to carcinogens that are similar to those found in tobacco smoke. This study also supported by another study done on cooking methods reviled increase of risk for breast cancer was associated with use of smoked food [157].

Our study related to source of fuel for cooking was also in agreement with a review conducted on a feasible correlation between air pollution and breast cancer risk. Based on their finding, even though, the mechanisms for how air pollution has effect on the occurrence or progression of breast cancer is unknown, but because the relationship between breast cancer and air pollution was determined, action for preventive efforts to improve health in females and quality of their

life to protect them from air pollution is necessary, especially in patients who are at high risk of advancing breast cancer [158].

In this study, the odds of breast cancer were lower among women who had an average duration of strenuous exercise of less than 5 hours per week; however, the association was not significant. Women who engaged in moderate physical activity for less than 5 hours per week had a lower risk of breast cancer than those who had no history of physical activity (AOR: 0.29, 95% CI: 0.159–0.541, P < 0.001). This result is comparable to that of a UK study that found a link between physical activity and a lower risk of breast cancer [159]. A systematic review and meta-analysis done in China that found a strong link between physical activity and a lower risk of breast cancer [160] also supported this study. More over this study was also in agreement with another study revealed a sound scientific evidence links greater physical activity with decreased breast cancer risk [145].

Only 5.0% of cases and 2.9% of controls in the current study had menarche before the age of twelve. When compared to what was considered to be a significant earlier age at menarche (< 12 years), late menarche (>15 years) was a protective factor for breast cancer. A study conducted in Morocco [133] backed up this conclusion. However, there was no association between ages at first birth, which was not comparable with a study done in Morocco [133]. Additionally, it was also found that 19 (8.3%) of cases and 4 (1.7%) of the controls had prior breast surgery. Women who had benign breast disease might have been associated with an increased risk of future breast cancer. In our study, breast cancer risk was seven times higher in women who had had benign breast surgery in the past. An investigation carried out in Malaysia supports this conclusion [150].

Additionally, we also found that the odds of breast cancer were 1.99 times higher among post-menopausal women (AOR: 1.99, 95% CI: 1.20–3.29). This result is comparable to a Malaysia study that found post-menopausal women had a 52% higher risk of breast cancer [150]. On the other hand, oral contraceptive use was not significantly associated with breast cancer. Though similar studies conducted in the United Kingdom and Jordan did not support our finding, they reported that women who have used hormonal contraception have a higher risk of developing breast cancer [161,162]. The type and length of contraception used, which may affect the risk of

breast cancer, may be the cause of this difference. Furthermore, there was no statistically significant correlation between breast cancer and parity or duration of breastfeeding, which is consistent with an Indian study [143].

6.4. Chemotherapy Adherence of Breast Cancer Patients (Paper IV)

A total of 164 women with breast cancer patients were participated in this study. Based on residence, the majorities (72.6% of women) were from urban areas, which were not compatible with the study done in rural Ethiopia (21%); this might be due to the focus of that study, which was conducted in the rural part of Ethiopia [102]. The mean age of study participants was 41.99 $\pm$ 10.9 years, which was lower than a study done in Iraq [50]. Nearly half (48.2%) of women were less than 40 years of age, which was comparable with a previous study done in Ethiopia [27]. It was also found that 90.9 % of women were married, which was comparable with studies done in rural Ethiopia (93%) [98] and Nigeria (70%) [163].

In our study, 137 out of 164 women (83.5%) adhered to their chemotherapy regimens, and 27 (16.5%) of the women stopped their chemotherapy before it was finished for a variety of reasons. This finding was lower than a study done on adherence to intravenous chemotherapy in African-American and Caucasian women, which revealed that 90% of breast cancer women were adherent to their chemotherapy [164]. This difference could be due to the study being done among early-stage breast cancer patients, which might increase patient's willingness due to the higher probability of a good outcome for early-stage cancer. The other possible reason could be that the study participants might have a better chance to get treatment access within a short time due to better infrastructure and adequate health facilities. However, it was comparable with the same study done on Caucasian participants, where adherence was 87.5% and 82.4% for African American participants [164].

However, this finding was lower than another study done in the USA, which reported that 88.1 percent completed the prescribed therapy. This difference could be due to the better infrastructure of the study setup, and the study was focused on early discontinuation of chemotherapy in women with breast cancer [165]. In addition to better infrastructure, their non-metastatic breast cancer status might contribute to this higher level of adherence. As indicated

before, severity of illness or advancement of their disease was the main factor that determined the level of adherence in our study. Similarly, our finding was higher than a study done in Indonesia, which found that only 56% of breast cancer patients had good adherence to chemotherapy. This difference could be due to the fact that in our study, good adherence is defined based on an 80% cutoff. On the other hand, an Indonesian study defines good adherence as when patients attain 90–100% of their prescribed chemotherapy [166]. However, this study was comparable with a study done in the USA, which found that of 7,399 patients, 1,222 (16.5%) were non-adherent [167].

It was also found that 52.0 % of women earned less than 2000 Ethiopian Birr per month. However, the level of adherence was not significantly different based on monthly income. Regarding menopausal status, 55% of women were on premenopausal status, which was comparable with a study done in rural Ethiopia (47%) [102]. In addition, the level of adherence was higher among postmenopausal women compared to their counterparts.

Moreover, the level of adherence was higher among women who had a family history of breast cancer compared to women without a family history of breast cancer. This may be because women with a family history of breast cancer may already be aware of how serious the condition is and how crucial it is to start and finish treatment as soon as possible. It was also found that the level of adherence was almost similar among women who had a history of smoking as well as drinking alcohol. This might be due to the fact that we found only 3 study participants had a history of smoking, which might not have made a significant difference. In addition, among women who had a history of alcohol consumption, the majority of them had consumed alcohol occasionally and in very small amounts or volume.

Regarding the clinical characteristics of study participants, the majority of women (44.5%) had stage III tumors at diagnosis. Similarly, ductal carcinoma was the most common histology, which was comparable with a previous study done in Ethiopia [113]. However, there was no difference in level of adherence across tumor grade or tumor pathology or histology. Our study also found that the majority (63.4%) of patients recommended eight courses of chemotherapy, which was not comparable with a study done in Nigeria (21.0%) [168]. This difference might be due to the different clinical conditions of patients and the different treatment strategies of the

countries. There was a significant association between breast cancer and courses of recommended treatment. This might be due to the fact that six courses of chemotherapy were planned as palliative care for most of the patients, and this may affect patients' adherence due to the severity of their illness, since severity of their illness was the main identified reason for non-adherence.

This study also revealed that factors related to non-adherence to chemotherapy were assessed. However, the reason for non-adherence was unknown for a significant number (29.1%) of patients. This is because it was difficult to access the patients through their phones in order to know their reason for non-adherence and their current status. This might be due to death, since there are a significant number of patients who have planned for chemotherapy but are excluded due to death before starting chemotherapy. Among a total of 27 non-adherent women, the majority (33.3%) did not adhere to their treatment regimen due to the severity of their illness. On the other hand, 4 out of 27 (14.8%) women did not adhere to their treatment due to financial reasons. This finding was not comparable with a study done in Nigeria, which revealed that financial constraints were the main reasons for non-adherence to chemotherapy for 61% of the patients [168]. This difference could be due to the fact that the focus of the Nigerian study was among 100 non-adherent women, which might explore the potential reasons for non-adherence.

6.5. Survival status of breast cancer patients (Paper V)

In our study, survival rates were examined for a total of 402 breast cancer patients. Of which 233 (58%) were dead and 169 (42%) were censored at the end of the study. Based on place of residence, almost half of patients were Addis Ababa residents, which was comparable with an earlier study done in Ethiopia [113]. The median age of the study participants was 43 $\pm$ 11.27 years. The majority of breast cancer patients were found to be under the age of 40, which was comparable with studies done in different regions of Ethiopia [23, 128,129]. However, the median age of study participants was 53 and 45 years in two different studies conducted in Sudan [169, 170]. This result was also in line with a study done in Pakistan, which found that the majority of study participants were younger than 50 [171]. However, this finding was lower than previous studies conducted in other developing and developed countries [105,172]. This

discrepancy may be due to Ethiopia's population characteristics, which show that its youth population is generally higher than that of other nations.

Our study showed comorbidity was found only among 30 (7.5%) study participants. Regarding the tumor side, almost half (49.8%) of patents had the left tumor side, which was comparable with a study done in Nigeria [163]. Moreover, this study also indicated that more than half, 206 (51.2%) of patients, were stage III at diagnosis, which was comparable with studies done in Sudan [169,170]. However, it is lower than a study done in Addis Ababa, where 71% of patients were stage III [113]. This difference could be due to the fact that the focus of that study was only on stage one, two, and three patients. As a result, since the majority of Ethiopian patients visit health facilities at an advanced stage, the number of patients with stage one and two are very small [113]. On the other hand, this finding was not supported by a systematic review conducted in Latin America and the Caribbean, which revealed that nearly 41% of women were diagnosed in stages III–IV [173]. This difference could be due to the fact that if there is better screening and treatment access for women, the incidence of advanced stages might decrease. The other possible difference could be that Ethiopian patients were treated for advanced cancer due to patient delay as a result of illiteracy, lack of health care access, financial constraints, inadequate diagnostic facilities, poorly structured referral, and seeking traditional healers, as described by different studies [20, 25,26]. However, the finding of this study is supported by a similar study done in sub-Saharan Africa on access to care in Ghana, Kenya, and Nigeria, which found that patients with breast cancer treated in tertiary facilities in sub-Saharan Africa lack access to timely diagnosis and modern systemic therapies [174].

In this study, most of the patients, 332 (82.6%), were diagnosed with ductal carcinoma, which was comparable with a similar study done in Ethiopia [118]. It was also supported by similar studies done in Sudan [170] and Nigeria [163], since majority of breast cancers were originated from the duct of the breast. This study also found that the mean and median survival times of patients were 68.84 (95% CI: 64.27-73.42) and 61.97 (49.72–74.22) months, respectively. Moreover, this study also indicated that the majority of study participants, 137 (34.1%) and 139 (34.6%), had grade II and undifferentiated grades, respectively. This result was comparable to that of a study conducted in Ethiopia [113].

We also found that 111 (27.6%) of the study participants had metastasis tumors to distal organs at diagnosis, of which the majority, 42 (37.8%), had lung metastasis. In addition, the study also found that the mean tumor size was 4.92 $\pm$ 4.22 cm. This finding was consistent with a study conducted in Ethiopia [113].

There was no significant relationship between tumor size and histologic type with breast cancer survival. For the majority, 317 (78.9%) of patients, primary treatment was surgery; this finding was lower than a study done in Addis Ababa [118]. This difference could be due to surgery being used as the primary treatment, and some women might be operated on after other forms of treatment, such as chemotherapy. On the other hand, the majority of 362 (90.5%) were treated with chemotherapy, which was comparable with a study done in Addis Ababa, which found that 782 of 893, or 87.5%, of patients received chemotherapy [113].

Our study found that the median follow-up time was 52.8 months and the median survival time was 61.96 months. The one-, two-, three-, five-, and ten-year survival rates were 85%, 75%, 62%, 50%, and 34%, respectively, according to life table analysis. This finding is much lower than the systematic review conducted on the global and regional survival rates of women with breast cancer. Globally, women with breast cancer had survival proportions of 0.92, 0.75, 0.73, and 0.61, respectively, over the course of one, three, five, and ten years [175]. Furthermore, the result of this study was also lower than the study conducted in Iran, which reported that the breast cancer-specific survival proportions for one-, two-, three-, five-, and ten-years were, respectively, 0.92, 0.88, 0.84, 0.77, and 0.65 [105]. The level of socio-economic development between countries, the age structure of the study population, the stage at diagnosis of health service access, the awareness of patients towards breast cancer, the accessibility of health services, and the infrastructure of health facilities could be associated with this wide range in the survival of patients.

However, our finding is somehow comparable with a study done on breast cancer survival in sub-Saharan Africa, which revealed that even though there were variations in breast cancer survival across different sub-Saharan countries, the overall relative survival of breast cancer patients was 86.1%), 65.8%, and 59.0% at year one, year three, and year 5, respectively [106].

We found that the two- and five-year survival rates were 75% and 50%, respectively, which is comparable with a study done in Addis Ababa, which found that survival was 74% after 2 years and 46% after 5 years [113]. Since, Ethiopian patients had treatment at an advanced stage of their diseases [20. 25, 26], which is the main determinant of survival.

Our study showed younger women had worse survival rates compared with older women. This finding was not supported by a similar study done in Iran, which reported that older individuals (≥50 years) had significantly worse survival [105]. Another study from Poland also indicated that older women with breast cancer were treated similarly to younger patients but had significantly worse chances to survive [176]. This difference could be due to the fact that large percentages of our study participants were found in younger age groups.

Based on the Kaplan Meier analysis, even though there was no significant difference, patients living outside Addis Ababa had lower median survival compared with patients living in Addis Ababa (55.50, 95% CI: 43.10–67.89, P = 0.431). This lower survival could be due to the distance to the referral cancer center and a lack of adequate information among rural women. In addition, women who had grade three or undifferentiated tumors had a lower chance of survival as compared with women with grade one tumors, which was comparable with a study done in Addis Ababa [113].

According to bivariate Cox regression, women with stage four had a 7.73-fold higher death rate compared with women with stages one and two of breast cancer. Similarly, women with grade three or undifferentiated tumors had 1.97-times higher risk of death compared with women with grade one tumors. It was also found that women who were not treated with surgery had significantly worse survival compared with patients treated with surgery. This finding was supported by a study done in Riyadh, Saudi Arabia [177].

It was also found that women who did not receive radiotherapy or hormone therapy had worse survival rates compared with patients who received those treatments. This finding was supported by a study done in Mexico that revealed that women who did not receive radiotherapy had an increased risk of breast cancer death relative to those who did [172]. Similarly, patients who had unknown chemotherapy and hormone therapy status had had significantly worse survival

compared with those treated with chemotherapy and hormone therapy. This could be due to the fact that patients with an unknown status may probably die as a result of their illness. In general, patients with their primary treatment being surgery had better survival, which could be due to the stage of their disease since surgery is usually conducted for early stages of disease as compared to advanced stages of disease.

According to multivariable Cox regression, stage of disease at diagnosis, metastasis status, and treatment status remained significantly associated with survival after the effects of confounding variables were controlled. Patients with stages three and four had significantly worse survival. Similarly, patients with metastases had 1.79 times worse survival as compared to patients without metastases. This finding is comparable with a similar study done in China, which found that patients with metastases showed significantly poorer breast cancer-specific survival. Moreover, patients who had not been treated with hormone therapy and radiotherapy had significantly lower survival rates compared with patients that received those treatments.

Similarly, this finding was also supported by a similar study done in China, which found that patients with primary surgery and radiotherapy had significantly improved overall survival. Patients who underwent surgery as the first treatment option had a better prognosis than those who were treated first by chemotherapy. It might be due to a larger tumor size, because women with larger tumors or metastatic diseases at diagnosis were mostly treated with chemotherapy followed by surgery [106].

7. Validity and generalizability

Since study participants came from different parts of the country, the findings of the study could be representative. This study applied different study designs, and in all designs, a large and adequate sample size was used in order to maximize the representativeness of the study. Moreover, all the data collectors (medical laboratory technologists, BSC nurses, oncology nurses, and oncology residents) were experts in the subject area and had experience collecting appropriate data and blood specimens. In addition, intensive training was given to all of the data collectors in order to maximize the quality of the data for the different study designs considered in this study.

There was daily supervision in order to avoid missing and incomplete data. All data collection tools were appropriate in order to accurately address the study objectives. Moreover, the tools were also translated to the local context (Amharic language), and translators were used for those who did not speak Amharic language in order to address the study objectives. Moreover, the tools were also translated to the local context (Amharic language), and translators were used for those who did not speak Amharic. Especially for the case-control study, in order to avoid recalling bias, different social events were used to remember their past exposures.

A confounder is an exposure external to our hypothesis that biases our measure of association unless it is controlled. When we compare our exposed population with the unexposed comparison group, the disease outcome will be different in the two groups even if the exposed had not been exposed [178]. In order to avoid the effect of confounding variables at the design phase, appropriate selection of study participants (including cases and controls) has been made. In addition, different statistical tests were applied during the analysis phase.

Bias is an error in the design or execution of a study that produces results that are consistently distorted in one direction because of nonrandom factors. Bias can occur in randomized controlled trials but tends to be a much greater problem in observational studies [179]. In order to limit bias, inclusion and exclusion criteria were applied during the selection of study participants. Furthermore, in order to avoid selection bias only female cases and controls were included in the study.

In addition, all measurements, definitions, and categorizations of variables were based on pre-established international standards. Suitable statistics and statistical models have been used based on previous similar studies conducted in different areas. For the determination of the hematological profile, paper one, since analysis of the blood in a different laboratory may produce different results because of systematic error, all hematological parameters were conducted in one laboratory. This is important to avoid bias and maximize internal validity.

Chance refers to the random distortion of the observed association between exposure and the outcome of interest due to sampling variability [180]. In this study, the role of chance was assessed by significance testing at $P < 0.05$, (95% confidence interval).

8. Strengths and limitations

8.1. Strengths

In this study, the main strength is the use of combining both clinical and public health research for different study objectives. In addition, the use of different experts (professionals with specialization in hematology and immunohematology for laboratory analysis, BSc nurses, oncology nurses, and oncology residents for data collection) adds to the strength of this study. Moreover, breast physical examinations were conducted by experienced female oncology residents in order to avoid fear and discomfort among study participants. Study participants with breast mass were advised for further checkups and screening for early diagnosis and treatment. During examination of hematological parameters, in order to maximize the quality of the laboratory test, standard operating procedures and internal quality controls were highly maintained on daily based. All collected blood specimens were analyzed on the same day of sample collection. For the measurement of adherence and survival, repeated phone calls were made until we had appropriate evidence.

8.2. Limitations:

This study might have some limitations. Since this study is a hospital-based study, it may not be representative of the general population. The other limitation could be that even though a breast physical examination has been made by an experienced physician, it may not be highly sensitive enough to detect potential breast mass.

The findings of our study were based on self-reporting, which could have introduced recall biases regarding their past exposure to different possible risk factors. That may result in underreporting the outcome of the study. The other most important limitation could be that, due to the limited time and budget it was difficult to conduct further analysis in different geographical locations and ethnic groups in order to explore potential risk factors.

Regarding measurement of adherence, since it was difficult to get non-adherent women, we could not explore different personal and health service-related factors that can affect the adherence level of breast cancer patients. There would be potential bias in the data collected

using telephone interviews and imprecise answers about adherence by relatives of deceased patients. In addition, factors associated with non-adherence were analyzed based on the baseline data, which was mainly focused on patient-related factors. In addition, sample size was not calculated for measurement of adherence. Thus, adherence was simply measured among those patients included for the case control study.

For the analysis of survival, data for demographic variables were missing due to incompatibility in the patient files. Moreover, since the last date of diagnosis was not recorded during data collection, it was difficult to analyze the data, which had unknown outcomes. In addition, due to some changes in telephone registries, it was difficult to find some study participants or their families in order to get the patient's status or outcome. As a result, a significant number of records and study participants were excluded from the analysis due to a lack of patient outcomes. As immunohistochemistry was not available, the biology of the tumor, which has implications for treatment and outcome, was not addressed in this study.

9. Conclusions

This study observed that most breast cancer patients were young, and there were a significant number of breast cancer cases under 30 years of age. Moreover, nearly half (43%) of breast cancer cases were illiterate or had low monthly income. Concerning hematological parameters, the mean hemoglobin, red blood cell count, packed cell volume, mean corpuscular volume, and mean corpuscular hemoglobin concentration values were significantly lower among cases compared to controls. On the other hand, some hematological parameters, like platelet count, are significantly higher among cases, which might be due to the progression of their disease. Moreover, anemia and thrombocytosis were also observed as major hematologic abnormalities among breast cancer patients.

Our study also indicated that the majority of cases and controls had O-positive blood groups. Similarly, 117 (92.7%) of cases and 214 (93%) controls were Rh positive. Even though some previous studies reported significant associations between the ABO/Rh blood group and breast cancer risk, our study added to the body of evidence that demonstrated no significant association between the ABO/Rh blood group and breast cancer risk.

We found that sociodemographic, lifestyle, anthropometric, and reproductive risk factors were assessed. The finding indicated that the odds of breast cancer decreased among educated and employed women. In addition, since most breast cancer patients lose weight as a result of the progression of the disease, the odds of breast cancer are significantly lower among obese women as compared with underweight women. Regarding lifestyle factors, the odds of breast cancer were higher among women who consumed solid oil and women who used wood or animal dung as a source of fuel. This finding indicated that there is a need to promote alternative fuel sources, especially for rural women. However, the odds of breast cancer decreased among women who had moderate physical exercise, less than 5 hours per week. Besides, the odds of breast cancer were significantly higher among women with early menarche, post-menopausal women, and women with previous benign breast surgery.

The results of the adherence assessment showed that the majority of patients (83.5%) were in good adherence with their chemotherapy. On the other hand, a total of 27 (13.5%) breast cancer patients were considered non-adherent to chemotherapy. The severity of illness, distance from the cancer referral centers, and regimen of chemotherapy were significantly associated with non-adherence.

Regarding survival analysis, 169 (42%) patients were alive (censored), and 233 (58%) patients died. The overall median survival time was 61.96 (95% CI: 49.71–74.41) months. The overall one, two, three, five-year, and 10-year survival proportions were 85%, 75%, 62%, 50%, and 34%, respectively. In general, in this study, survival was relatively poor, and it was associated with women diagnosed with late-stage disease (stage III and stage IV), women who had metastasized tumors, and women who had unknown chemotherapy, radiation, and hormone therapy status.

10. Recommendations

Policy makers and the Ministry of Health

- This study found that there are modifiable factors associated with breast cancer. Therefore, it is essential to design appropriate lifestyle modification strategies like regular exercise, consumption of unsaturated fatty acids, and other modifiable risk factors that may contribute to preventing breast cancer. Moreover, there is a need to design appropriate intervention strategies to educate women about lifestyle change or behavior modification to decrease their breast cancer risk.
- Most breast cancer patients were diagnosed at an advanced stage of the disease. Even though, there is a national cancer prevention strategy it is not updated. This strategy also lacks comprehensive integration and coordination with the existing primary health care system. Therefore, there is a need to to have updated national cancer prevention atrategy as well as establish comprehensive cancer control plan, including, national breast screening program, especially for high-risk women, in order to promote early diagnosis and treatment.
- Financial constraints and distance from referral centers were the main detriments to chemotherapy adherence. Even though it is costy, government should expand optimal cancer diagnosis and treatment centers in order to maximize patients' access to health care services and minimize advanced stages of diseaseas much as possible.
- The Ministry of Health should give special emphasis to setting up different interventions or measres including a mass awareness campaign, early stage diagnosis, and initiation of treatment to reduce the advanced stage of breast cancer, since which are the most important determinant of survival.
- Based on the availability of resources, integrated and effective prevention and treatment strategies should be implemented at different health facility levels especially at primary health care level in order to address patient needs with adequate and skilled manpower.

Health care providers

- Healthcare providers should deliver adequate information about the importance and outcome of chemotherapy for their patients in order to maximize treatment adherence.
- It is also important that health care providers adequately encourage and monitor newly diagnosed women by sharing the experiences of successful women as a result of their treatment adherence through training or health education programs.
- In order to increase the level of adherence to chemotherapy, clinicians should be required to cover help gaps that could jeopardize patients' commitment to their treatment follow-up schedule.
- Since hematologic parameters are important predictors of treatment, health care providers should utilize such parameters and differentiate high-risk patients so as to obtain clinical benefits.

Women

- Women should check their breasts regularly and immediately request advice when they have a breast mass or any abnormality.
- All women, especially those 40 years of age and older, should practice regular screening and breast examination at least once per year.
- Breast cancer patients should strictly follow their treatment in order to improve their health conditions or outcomes.

Further searcher

- There are inconsistencies in the association between ABO blood group and breast cancer risk; further studies should be done with a large sample size, in a wider geographical location, and with diverse ethnic groups in order to establish the role of ABO blood group in the prognosis of breast cancer.
- Since Ethiopia is the home of different ethnic groups, further nationwide studies should also be done to explore the distribution of ABO/Rh antigen differences between various ethnic groups.
- In addition, since there are varieties of culture, food choice, feeding habits, physical activities, and other risk factors, it is important to conduct future studies with a larger

sample size, including different regions or diverse populations, in order to come up with more strong and representative evidence about potential risk factors for breast cancer.

- Even though there was a national “NCD STEPS survey” conducted in Ethiopia, there is a need to conduct more advanced and highly controlled study to explore various risk factors particular to breast cancer.
- Further research should be undertaken to investigate how different patient groups beliefs and potential factors may influence the level of adherence among breast cancer patients.

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13. Annexes

Annex I: Subject Information Sheet for Study Participants
Subject Information Sheet for breast cancer patients

Principal investigator: Fatuma Hassen

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1. Prof. Fikre Enkusilassie (AAU. School of Public Health)
2. Prof. Ahmed Ali (AAU. School of Public Health)
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5. Dr. Mathewos Assefa (AAU, Department of Oncology)
6. Dr. Aster Tesegaye (AAU, Department of Medical Laboratory Sciences)

Sponsor: Addis Ababa University

Title of Proposal: Epidemiology of Breast cancer: Risk factor, treatment adherence and outcome of breast cancer patients attending Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

Introduction

This is a research project on breast cancer, which is conducted among breast cancer patients and their respective controls that are free from breast cancer. The objective of this study was to assess risk factors, treatment adherence and outcome of breast cancer patients and respective controls attending Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

Now we are going to give you information and invite you to be part of this research. You may take some time to decide on whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research. This consent form may contain words that are new to you. If you read any words that are not clear to you, please ask the person who gave you this form to explain them to you.

Participants (breast cancer cases) will be selected from all adult women attending the oncology department of Tikur Anbesa Specialized Hospital and respective healthy controls will be selected from care givers. Participant selection will be voluntary.

Purpose of the research

Currently breast cancer is one of the common cancers in Ethiopia. However, the majority of the patients come to health facility at advanced stage of the disease as a result of this most patients have poor treatment adherence and poor outcome. In this study we are planning to assess the epidemiology of breast cancer in order to identify risk factors, treatment adherence and outcome. Information drawn from this research may contribute to design prevention strategies, to modify lifestyle, improve adherence and outcome of patients of breast cancer. The result of laboratory tests will be notified for the study participants, especially if the result is significant.

Type of Research Intervention

The research will be conducted using structured questionnaire and taking blood specimen from each study participants by trained laboratory professionals. Since blood specimen will be collected through safe and sterile laboratory materials, there will not be any harm related to the procedure. In addition, longitudinal data (from 4-6 month) will be collected from each breast cancer patients in order to measure their level of adherence and associated factors. Each study participants will be expected to respond to all questions, provide blood specimen and anthropometric measurement. Taking blood sample is a painless procedure where a needle is inserted in your vein in order to collect 10ml blood. The overall process will take 30 to 45 minutes. You will not have additional appointment as a result of this study.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this hospital will continue and nothing will change. If you choose not to participate in this research project, you will be offered the treatment that is routinely offered in this hospital.

Risks/Discomforts:

There is no anticipated discomfort for those participants as a result of participating in this study, so risk to participants is minimal.

Benefits

There may not be any direct benefit for you but your participation is important as it help us find the answer to the research question which in turn benefits the society especially women in the future. Your participation will help in order to design prevention and control measures of breast cancer.

Confidentiality

Your records will be kept confidential and will not be released without your consent except as required by law. All information which is collected about you during the course of the research will be kept on a password protected database and is strictly confidential. Any information about you which leaves the research team will have your name and address removed so that you cannot be recognized from it. We will replace this information with a code. Even the finding of this study will be published and communicated in different conference, your name/ identity will not be described.

Storage and transfer of samples

Collected blood samples will be labeled with a code and analyzed at laboratory. The sample will be stored for short period of time if test repeat or result check is required as needed. In addition, sample storage is helpful if additional test is required based on the result of the test.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this hospital in any way. You will still have all the benefits that you would otherwise have at this hospital. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this hospital will not be affected in any way.

Whom to Contact

If you have any questions, you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact the investigators and the ethics committee for further information at the following address;

1. Fatuma Hasssen: Tel. +251- 911418062
2. Prof. Fikre Enkusilassie: Tel. +251- 912 45 97 07
3. Prof. Ahmed Ali : Tel. +251- 911 68 43 99
4. Dr.Adamu Addissie : Tel. +251- 911 404954
5. Dr. Girma Taye : Tel. +251- 911 76 99 26
6. Dr. Matwos Assefa : Tel. +251- 911 24 05 21
7. Dr. Aster Tesegaye : Tel. +251- 911 69 60 85

Institutional Review Board, CHS: Tel. +251- 11 8- 96 13 96

Subject Information Sheet for healthy controls/care givers

Principal investigator: Fatuma Hassen (AAU, Department Medical Laboratory Science)

Supervisors:

1. Prof. Fikre Enkusilassie (AAU. School of Public Health)
2. Prof. Ahmed Ali (AAU. School of Public Health)
3. Dr.Adamu Addissie (AAU. School of Public Health)
4. Dr. Girma Taye (AAU. School of Public Health)
5. Dr. Mathewos Assefa (AAU, Department of Oncology)
6. Dr. Aster Tesegaye (AAU, Department of Medical Laboratory Sciences)

Sponsor: Addis Ababa University

Title of Proposal: Epidemiology of Breast cancer: Risk factor, treatment adherence and outcome of breast cancer patients attending Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

Introduction

This is a research project on breast cancer, which is conducted among breast cancer patients and respective healthy controls that are free from breast cancer. The objective of this study is to assess risk factor, treatment adherence and outcome of breast cancer patients and respective controls attending Tikur Anbessa Specialized Hospital, Addis Ababa.

Now we are going to give you information and invite you to be part of this research. You may take some time to decide on whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research. This consent form may contain words that are new to you. If you read any words that are not clear to you, please ask the person who gave you this form to explain them to you.

Breast cancer patient women care givers which are free from breast cancer will be selected from all adult women attending the oncology` department, Tikur Anbesa Specialized Hospital. Participant selection will be voluntary.

Purpose of the research

Currently breast cancer is one of the common cancers in Ethiopia. However, the majority of the patients come to health facility at advanced stage of the disease as a result of this most patients have poor treatment adherence and poor outcome. In this study we are planning to assess the epidemiology of breast cancer in order to identify risk factors, treatment adherence and outcome. Information drawn from this research may contribute to design prevention strategies, to modify lifestyle, improve adherence and outcome of patients of breast cancer. The result of laboratory tests will not be notified for the study participants, it is only used for research purpose.

Type of Research Intervention

Breast physical examination will be done by experienced physician in order to select study participants which are free from breast cancer. After physical examination in-depth interview will be conducted with breast cancer free controls. Finally blood specimen will be collected from each study participants by trained laboratory professionals. Since breast physical examination is a painless procedure and blood specimen will be collected through safe and sterile laboratory materials, there will not be any harm related to the procedure.

Each study participants will be expected to respond to all questions, provide blood specimen and antropometric measurement. Taking blood sample is a painless procedure where a needle is inserted in your vein in order to collect 10ml blood. The overall process will take 30 to 45 minutes. You will not have additional appointment as a result of this study.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this hospital will continue and nothing will change. If you choose not to participate in this research project, you will be offered the treatment that is routinely offered in this hospital.

Risks/Discomforts

There is no anticipated discomfort for those participants as a result of participating in this study, so risk to participants is minimal.

Benefits

The benefit of participating in this study will be, if study participants, will have breast mass, referral issues will be linked and facilitated for further diagnosis and treatment. In addition, your participation is also important as it help us find the answer to the research question which in turn benefits the society especially women in the future. Your participation will help in order to design prevention and control measures of breast cancer.

Confidentiality

Your records will be kept confidential and will not be released without your consent except as required by law. All information which is collected about you during the course of the research will be kept on a password protected database and is strictly confidential. Any information about you which leaves the research team will have your name and address removed so that you cannot be recognized from it. We will replace this information with a code. Even the finding of this study will be published and communicated in different conference, your name/ identity will not be described.

Storage and transfer of samples

Collected blood samples will be labeled with a code and analyzed at TASH, The sample will be stored for short period of time if test repeat or result check is required as needed.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this hospital in any way. You will still have all the benefits that you would otherwise have at this hospital. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this hospital will not be affected in any way.

Whom to Contact

If you have any questions, you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact the investigators and the ethics committee for further information at the following address;

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5. Dr. Girma Taye : Tel. +251- 911 76 99 26
6. Dr. Aster Tesegaye : Tel. +251- 911 696085
7. Dr. Matwos Assefa : Tel. +251- 911 24 05 21
8. Institutional Review Board, CHS: Tel. +251- 11 8- 96 13 96

Annex II: Consent form (for both breast cancer patients and controls)
For literate participants

I have read the foregoing information, or it has been read and understood to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Name of Participant _____Sign._____ Date _____

For illiterate participants

A literate witness must sign (if possible, this person should be selected by the research team). Participants who are illiterate should include their thumb-print as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has opportunity to ask questions. I confirm that the individual has given consent freely.

Name of witness_____ and Thumb print of participant

Signature of witness _____ Date _____

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the purpose of the study and the processes and procedures to be undertaken.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant will be answered correctly and to the best of my ability. I confirm that the individual will not be forced into giving consent, and the consent will be given freely and voluntarily.

A copy of this informed consent form will be provided to the participant.

Annex III: Questionnaire

I. Questionnaire used to measure risk factors of breast cancer

1. General information

1.1 Study participant identification code: _____

1.2 Date of interview: _____

1.3. Place of interview: _____

1.4. Card No: _____

1.5. Telephone No: _____

1.6. Name of Researcher/person taking the consent_____Signature_____ Date ____

No	Questions	Responses
100	**SECTION A DEMOGRAPHIC INFORMATION**	
101	Age	_____ in Years
102	Religion	1) Orthodox 2) Muslim 3) Protestant 4) Other (Specify
103	Ethnicity	1) Oromo 2) Amhara 3) Tigre 4) Other specify_____
104	Marital status	1) Single 2) Married 3) Divorced 4) Widowed 5) Other specify_____
105	Educational level	1) Illiterate 2) Read and write 3) Elementary education (1-8) 4) secondary education (9-12) 5) College diploma/degree and above
106	If married, Educational level of your husband?	1) Illiterate 2) Read and write 3) Elementary education (1-8) 4) secondary education (9-12) 5) College diploma/degree and above
107	Occupation	1) Farmer 2) House wife 3) Student 4) Merchant 5)

		GOV. employee 6) Others_____
108	Residence	1) Rural 2) Urban Zone _____ District _____
109	If out of Addis, Distance from Cancer center?	_____ KM
110	Family monthly income	In Eth. Birr (_____)
111	Your home	1. My own 2. Rent
200	**Part 2. Questions related to reproductive health**	
201	If you are married, Age at first marriage	_____ years
202	Have you ever been pregnant?	1. Yes 2. No
203	have you ever gave birth to a life born infant	1. Yes 2. No
204	How many live births have you had?	Number _____
205	How old were you when your {first) child was born?	1. Age_____ 2. DK
206	Did you breastfed any of your children?	1. Yes 2. No
207	If yes, how long did you breast-feed, including mixed feeding?	_____
208	Did you have miscarriages or abortions?	1. Yes 2. No
209	If YES, how many?	_____Number of abortion
210	How old where you when your menstrual cycle began?	2. Age_____ 3. Never menstruated 4. Do not know/Do not remember
211	Has your menstrual cycle stop permanently?	1. Yes 2, No 3. Never menstruated
212	How old were you when they completely stopped?	1. _____Age in years 2. Do not know/Do not remember

213	What was the reason for this stop?	1. Due to menophose 2. Due to surgery 3. Other specify_____
214	Have you had an operation to remove a lump sum from your breast that was found to be NONCANCEROUS?	1. Yes 2. No
215	If yes, how many of this operation have you had?	1. Number of operation_____ 2. Do not know/Do not remember
216	If yes, how old were you when you had the first operation?	_____Years 2. Do not know/Do not remember
217	Have you ever used birth control pills?	1. Yes 2. No
218	If yes, How old when you started using birth control pills?	1. _____ Age 2. Do not know/Do not remember →Q 300
219	Altogether how long did you use birth control pills? Include any break in usage that lasted less than one month	1. Days_____ 2. Months _____ 3. Years _____ 4. Other specifies _____ 5. DK
300	**Questions related to menopausal and hormone replacement therapy (this hormone can be administered orally or intravenously, but does not include drug intra urine drug)**	
301	Have you taken estrogen, progesterone or other female hormones for menopause, that is, prescription hormone replacement therapy or HRT?	1. Yes 2. No → 400
302	If yes, how old were you when you first used female hormones for menopause?	_____Years
303	Were you currently using these female hormones for men?	1. Yes 2. No
304	Are you currently taking female hormones for menopause?	1. Yes 2. No
305	If No: at what age did you stop taking female hormones for menopause?	
306	For how many months or years have you taken female hormones for menopause?	___ months OR____ yrs.
307	What were the hormones you mainly used during that time?	1. Progesterone only 2. Estrogen only

		3. Progesterone and estrogen 4. DK the Brand 5. Other specify_____ ___
400	**Fmily History of Cancer**	
401	**These next questions are about your natural or birth mother and father. Do not Include step or adopter parents**.	

Family history (age at diagnosis is needed- please estimate if unsure)

1**. Mother:** Breast cancer ____ Ovarian cancer : _____Age at diagnosis: _____

2. **Any of sisters**: Breast cancer ____ Ovarian cancer : _____Age at diagnosis: _____

3. **Any of grandmothers**: Breast cancer ____Ovarian cancer : _____Age at diagnosis: _____

4. **Father** Breast cancer ____Ovarian cancer : _____Age at diagnosis: _____

5. **Others:** Breast cancer ___ Ovarian cancer : _____Age at diagnosis: _____

500	**Personal behavior and life style related questions**	
501	Have you smoked cigarettes regularly that are at least one cigarette per day for 3 months or longer?	1. Yes 2.No
502	If Yes: How old were you when you first started smoking cigarettes regularly?	_____ Age in year
503	Are you currently smoking cigarettes regularly?	1. Yes 2.No
504	IF No: At what age did you stop smoking?	_____Age in year
505	For how many years or months did you smoke at least one cigarette a day?	_____months_____Years
506	During this time, how many cigarettes did you usually smoke in a day?	_____Number of Cigarette per day
507	Does/did someone smoke inside your living home/room?	1. Yes 2.No
508	If yes, how long does/did someone smoke inside your living home/room?	_____Months _____Years

509	What is your source of energy for cooking food?	1. Wood /animal dung 2. Electric 3. Charcoal 4 Cerrosin gas 5. Other specify_____
510	Do you have separate room for cooking food?	1. Yes 2.No
511	Have you consumed alcohol (such as beer, wine or hard liquor, including mixed drinks) regularly, that is, at least once per week for six months or longer?	1. Yes 2.No
512	If Yes, how old were you when you first started drinking alcohol at least once per week for six months or longer?	_____Years
513	Have you ever drunk alcohol?	1. Yes 2.No
514	If No, At what age did you stop drinking alcohol at least once per week?	_____years
515	For how many years or months did you drink alcohol at least once per week?	_____Months _____Years
516	During this time, how many glass or bottles of beer did you usually have in a week?	_____Glass _____Bottle
600	**Exercise and diet related question**	
601	How frequently consumed the following food items? Please put the following ("√□") Mark	

No	Types of food	A Once per day	B More than once per data	C 2-3 times per week occasionally	D Occasionally (e.g. holidays, special ceremonies)	E Never
601	Vegetables (Cabbage, tomato, etc.					
602	Fruit (orange, banana, etc.					
603	Meat (poultry. fish, etc.)					
604	Milk and milk product (Butter, yoghurt, cheese, etc.)					

605	Did you consume saturated oil?	1. No 2. Yes, always 3. Yes, some times
606	How often did you participate in streamers exercise activities or sport (e.g. swimming laps, aerobic, running,	1. Yes 2. No

	basketball, cycling on hills, racquet ball)	
607	If yes average hours per day, average months per year	_____hr./day ____month/year
608	How often did you participate in moderate exercise activities or sport (e.g. walking, golf, volley ball, cycling on level street, recreational tennis or soft ball)	1. Yes 2.No
609	If yes average hours per day, average months per year	_____hr./day ____month/year
700	**Question related to radiation exposure**	
701	Had you ever had x ray examinations that included the chest area	1. Yes 2. No
	If yes	

	Number of x ray examination	**Age at first examination**	**Frequencyof examination**
X ray examination that included the chest area			
Other specify			

800	**Anthropometrical measurement**	
801	Height at diagnosis (in meters)	
802	Weight at diagnosis (in kg) (not including pregnancy)?	
803	Body mass index at diagnosis (kg/m)	
900	**Laboratory result**	
901	Blood group	ABO: _____RH factor: _____
902	Hemoglobin	_____gm/dl
903	PCV	_____%
904	White blood cell count	_____mm^3
905	Red blood cell count:	_____mm^3
906	Platelet count	_____mm^3

Interview Date:_____ Interviewer's Name_____ Signature

II. Questionnaire used to measure treatment adherence on chemotherapy adherence

100	**Socio demographic characteristics**	
101	Age	_____ in years
102	Religion	1. Orthodox Christian 2. Muslim 3. Protestant 4 Other (Specify
103	Marital status	1. Single 2. Married 3. Divorced 4. Widowed 5. If other specify_____
104	Educational level	1. Illiterate 2. Read and write 3. Elementary education 4. Secondary education 5. College diploma/degree
105	Occupation	1. Farmer 2. House wife 3. Student 4. Merchant 5. GOV. Employee 6) Others
106	Residence	1. Rural 2.Urban
107	Educational Level of your husband?	1. Illiterate 2. Read and write 3. Elementary education 4. Secondary education 5. college diploma/degree

Part 2 Medical history

No	**Questions**	**Response**
201	Patient of first treatment	_____
202	Tumor side	1. Left 2. Right
203	Histology	1. Ductal 2. Lobular 3. Mixed 4. Other_____
204	Stage of cancer	1. I 2. II 3 III 4. IV 5. Undetermined
205	Week of treatment	1. Four 2. Six 3. Eight and above
206	Type of chemotherapy	
207	Has the patient missed any chemotherapy appointment since she first began chemotherapy	1. Yes 2. Yes
208	If yes how many times	1. One 2. Two 3. Three 4. Four and above
209	Reason for missed treatment	1. Social stigma 2. Cost of medications 3. Forget due to busy schedule 4. Other specify _____

III, Questionnaire used to measure treatment outcome of breast cancer patients treated at Tikur Anbessa hospital

No	Variables	Coding
	Code _____	**Patient card number _____**
100	**Socio demographic characteristics**	
101	Age at diagnosis	_____ In years
102	Religion	1. Christian 2. Muslim 3. Protestant 4 Other Specify_____
103	Marital status	1. Single 2. Married 3. Divorced 4. Widowed 5. Other specify_____
104	Educational level	1. Illiterate 2. Read and write 3. Elementary education 4. Secondary education 5. College diploma/degree and above
105	Occupation	1. House wife 2. Merchant 3 GOV. Employee 4) Others specify _____
106	Residence	1. Rural 2.Urban
107	Permanent Address	Region _____ zone_____ woreda_____ Town_____
108	Distance to if out of Addis Ababa	_____Kilometer
109	Menstrual status	1. Premenopausal 2. Post-menopausal 3. Un known
110	Blood group	1. A 2. B 3. AB 4. O 5. unknown
200	**Disease characteristics**	
201	Diagnosis date	_____(Date, month, Year)
202	Location of tumor	1. Central 2. Non central 3. Multifocal 4. Unknown 5. Not stated
203	Tumor side	1. Right 2. Left
204	Tumor size	_____
205	Grade	1. Well 2. Moderate 3. Poor 4. Not determined 5. not stated
206	Numbers of involved	_____

	lymph nodes	
207	lymph, vascular, neural invasion	1. No invasion 2. LVN invasion 3. Unknown
208	Multifocality	1. Unifocal 2. Multifocal
209	Estrogen receptor status	1. Positive Negative 3. Unknown
210	Progesterone receptor status	1. Positive Negative 3. Unknown
211	Is the patient being treated for a recurrence or new cancer?	1. New 2. Recurrence
212	Metastasis	1. No 2. To lung 2. To bone 3. Liver 4. Other specify _____
300	**Treatment characteristics**	
301	Primary treatment	1. Surgery 2. Radiation 3. Chemotherapy 4. Hormone therapy 5. No treatment
302	If surgery, type of surgery received	1 breast conserving surgery 2 Mastectomy 3. Other specify _____
303	Radiation therapy	1. Received 2. Not received 3. Unknown
304	Hormone Therapy	1. Received 2. Not received 3. Unknown
305	Radiation therapy	1. Received 2. Not received 3. Unknown
306	First hormone therapy	1. Tamoxifen 2. Toremifene 3. Anastrozole 4. Other specify _____
307	Extent of residual tumor	_____
308	Staging at time of the diagnosis	1. Stage I 2. Stage II 3. Stage III 4. Stage IV
309	Current status	1. . Live 2. Death
310	Cause of death	1. Breast cancer 2. Other specify_____

Name of data collector _____Date _____Signaturer _____

Annex IV: Subject Information Sheet for Study Participants (in Amharic)

በጡት ካንሰር ላይ ለሚደረግ ጥናት ለተሳታፊዎች የተዘጋጀ የጥናቱ ዝርዝር መረጃ

ሀ. ለጡት ካንሰር ታማሚዎች

ዋና አጥኚ፡ ፋጡማ ሀሰን (አአዩ፣ሕክምና ላቦራቶሪ ሳይንስ ት/ት ክፍል)

አማካሪዎች/ሱፐርቫይዘሮች

ነ. ፕ/ር ፍቅሬ እንቁስላሴ (አአዩ ፣ ህብረተሰብ ጤን ሳይንስ ት/ቤት)

2. ፕ/ር እህመድ አሊ (አአዩ ፣ ህብረተሰብ ጤን ሳይንስ ት/ቤት)
3. ዶ/ር አዳሙ አድሴ (አአዩ ፣ ህብረተሰብ ጤን ሳይንስ ት/ቤት)
4. ዶ/ር ግርማ ታየ (አአዩ ፣ ህብረተሰብ ጤን ሳይንስ ት/ቤት)
5. ዶ/ር አስቴር ጸጋየ (አአዩ፣ሕክምና ላቦራቶሪ ሳይንስ ት/ት ክፍል)
6. ዶ/ር ማቲወስ አሰፋ (አአዩ፣ የካንሰር ሕክምና ክፍል)

ስፖንሰር፡ አዲስ አበባ ዩኒቨርሲቲ (አአዩ)

የጥናቱ ርዕስ፡ በአዲስ አበባ ዩኒቨርሲቲ ጥቁር አንበሳ ሆስፒታል ካንሰር ህክምና ክፍል ለጡት ካንሰር ተጋላጭነትን የሚጨምሩ መንስኤዎች፤ ለሚደረገዉ ህክምና ያላቸዉ ክትትል እና ህክምና ዉጤታቸዉ ምን እንደሚመስልየሚደረግ ጥናት ነዉ::

መግቢያ

ይህ ጥናት በአዲስ አበባ ዩኒቨርሲቲ ጥቁር አንበሳ ሆስፒታል የጡት ካንሰር ህሙማን እና ከጡት ካንሰር ነጻ የሆኑ ህሙማን ላይ ሲሆን፤ የጥናቱ አላማ ለጡት ካንሰር ተጋላጭነትን የሚጨምሩ መንስኤዎች፤ ህሙማን ለሚደረገዉ ህክምና ያላቸዉ ክትትል እና ህክምና ዉጤታቸዉ ምን እንደሚመስልየሚደረግ ጥናት ነዉ::

አሁን ስለ ጥናቱ አስፈላጊ መረጃዎችን ከሰጠንዎት በኋላ በጥናቱ እንዲሳተፉ ጥሪ ዕናደርጋለን:: በጥናቱ ለመሳተፍ እንደአስፈላጊነቱ ጊዜ ወስደው በማሰብ ወይም ከሌላ ሰው ጋር በመማከር መወሰን ይችላሉ:: በዚህ የስምምነት ቅፅ ውስጥ አዳዲስ ወይም ሙያዊ ቃላት ሊገኙ ይችላሉ:: በመሆኑም ማንኛውም ግልፅ ያለሆነ ሃሳብ ሲያጋጥምዎ ቅፁን የሰጠዎትን ሰው ማበራሪያ መጠየቅ ይችላሉ::

የዚህ ጥናት ተሳታፊዎች በጥቁር አንበሳ ሆስፒታል የጡት ካንሰር ህክምና ለይ ያሉ አዋቂ ሴቶች ሲሆኑ፤ ከጡት ካንሰር ነጻ የሆኑ አስታማ ሴቶችንም የጨምራል:: በምርጫዉ ወቅት ሁሉም የጥናቱ ተሳታፊዎች ፈቃደኝነታቸዉን ተጠይቀዉ ይመረጣሉ::

የጥናቱ ዓላማ

በአሁኑ ጊዜ የጡት ካንሰር በተለይ እንደ ኢትዮጵያ ባሉ ታዳጊ አገሮች ውስጥ የተለመደ የጤና ችግር እየሆነ ይገኛል፡፡ ይሁን እንጂ ብዙዎቹ የጡት ካንሰር ታማሚዎች ወዴ ህክምና ተቋማት የሚመጡት በጣም ዘግይተዉ ስለሆነ ለሚታዘዝላቸዉ ህክምና ያላቸዉ ክትትል ፤ የህክምና ዉጤታቸዉ እና ከበሽታዉ ለመዳን ያላቸዉ እድል በጣም አነስተኛ ነዉ፡፡ በዚህ ምርምር ለማጥነት የታቀደዉ ለጡት ካንሰር ተጋላጭነትን የሚጨምሩ መንስኤዎችን፤ መለየት& ለሚደረገዉ ህክምና ያላቸዉ ክትትል ማየት፤ ህክምና እንዳከታተሉ የሚያግዷቸዉን ሁኔታዎች መለየት እና በህክምና ክትትሉ የሚያገኙትን ዉጤት ወይም የጤንነት ሁኔታ ለማወቅ ነዉ፡፡

በዚህ ጥናት የሚገኘዉ መረጃ ለወደፊት የጡት ካንሰርን፣ ለመከላከል፣ ታማሚዎች የተሻለ የህክምና ክትትል እንድኖራቸዉ እንድሁም ለጡት ካንሰር የሚያጋልጡ ሁኔታዎችን ለማስወገድ ይረዳል፡፡ የላቦራቶሪዉ ዉጤት ለተሳተፊዎች የሚገለጽ ሳይሆን ለጥናቱ ዓላማ ብቻ ይዉላል፡፡

ጥናቱ የሚካሄድበት መንገድ

ይህን ጥናት ለማድረግ ለእያንዳንዱ የጥናት ተሳታፊ የሚሆን መጠይቅ የተዘጋጀ ሲሆን በተጨማሪም 5 ሚሊ ሊትር የሚሆን የደም ናሙና ይሰበሰባል፡፡ የደም ናሙናዉ በሰለጠኑ የላቦራቶሪ ባለሙያዎች የሚሰበሰብ ሲሆን ለዚሁ ጉዳይ በተዘጋጁ እና ጽዱ በሆኑ የላቦራቶሪ እቃዎች ሥለሚሰበሰብ ሂደቱ ምንም ጉዳት አያስከትልም፡፡ በተጨማሪም የጡት ካንሰር ህሙማን ለሚኖራቸዉ ህክምና የላቸዉን ክትትል ለመለካት ከ4 እስከ 6 ወራት ተከታታይ መረጃዎች ይሰበሰባሉ፡፡ ከእያንዳንዱ ተሳታፊ የሚጠበቀዉ ለጥያቄዎች ምላሽ መስጠት፤ የደም ናሙና መስጠት፤ ክብደት እና ቁመት መለካት ይሆናል፡፡

የደም አወሳሰድ ሂደቱ ቀላል እና ህመም የሌለዉ ነዉ ሲሆን 10 ሚሊ ሊትር የደም ናሙና ይሰበሰባል:: ባጠቃላይ ጠቃሚ መረጃዎችን ለማጠናቀር ዕና የደም ናሙናዉን ለመሰብሰብ ከ30 እስከ 45 ደቂቃ ሊወስድ ይችላል፡፡ በጥናቱ ተሳታፊ በመሆንዎ ምክንያት ብቻ ለተጨማሪ ቀጠሮ እንዲመጡ አይጠየቁም፡፡

በፈቃደኝነት ላይ የተመሰረተ ተሳትፎ

በዚህ ጥናት ላይ መሳተፍ ሙሉ በሙሉ በርስዎ ፈቃድ ላይ ብቻ የተመሰረተ ይሆናል፡፡ ስለሆነም፣ መሳተፍ አና አለመሳተፍ

የርስዎ ነፃ ምርጫ ነው፡፡ በዚህ ጥናት ላይ ቢሳተፉም ባይሳተፉም፣ በዚህ የህክምና ተቋም የሚሰጠውን ህክምና ካለልዩነት

ያገኛሉ፡፡

ጉዳት

በዚህ ጥናት መሳተፍ ከመደበኛው የህክምና ሂደት የተለየ ምንም አይነት የተሳታፊዎችን ደህንነት ሊጎዳ የሚችል ተጨማሪ

ሂደት እይካሄድም፡፡ በጥናቱ በመሳተፍዎ ምክንያት የሚደርስብዎ አደጋ ወይም መንገላታት የለም፡፡ ስለሆነም በጥናቱ

መሳተፍ የሚስከተለው የነላ ጉዳት የለም፡፡

ጥቅም

ተሳታፊዎች ምንም አይነት ቀጥተኛ የግል ጥቅም ባያገኙም፣ እርስዎ በዚህ ጥናት በመአሳተፍዎ ጥናቱ ያነሳቸውን

ጥያቄዎች በመመለስ /በማገዝ ለወደፊት የሕብረተሰቡ በተለይም የሴቶችን ጤና ለመሻሻል ከፍተኛ አስተዋፅዖ ያደርጋል፡፡ ይህን በማድረገዎ የጡት ካንሰርን ለመቆጣጠር እና ለመከላከል በሚደረግ ጥረት የበኩለዎን አስተዋፅዖ የደርጋሉ፡፡

ምስጢራዊነት

ማናቸውም የጤናና ሌሎች በጥናቱ ምክንያት የሚገኙ እርስዎን የሚመለከቱ መረጃዎች በከፍተኛ ምስጢርነት የሚጠበቁ

ሆኖ በእርስዎ ፈቃድና ህግ በሚያዘው መሠረት ካልሆነ በስተቀር ለሌላ ወገን አይገለፁም፡፡ ስለ እርስዎ የተሰበሰበ መረጃ

በሙሉ በይለፍ ቃል በሚዘጋ የመረጃ ቋት ውስጥ የሚከማች ሲሆን፣ መረጃዎቹ ከጥናት ቡድኑ እጅ በሚወጡበት ጊዜ

የማንነት መገለጫዎች በሙሉ ለሌላ ሰው በማይታወቁ የምስጢር ኮድ ይቀየራሉ፡፡ የዚህ ጥናት ውጤት በህትመት ውጤቶች ላይ የሚወጣ ቢሆን ወይም በተለያዩ መንገዶች ለህዝብ የሚቀርብ ቢሆን የርስዎ ስም ወይም ማንነት በምንም አይነት መንገድ አይገለፅም፡፡

ናሙና ስለማከማቸት እና ስለማዘዋወር

የተሰበሰበው ናሙና ምስጢራዊ መለያ ከተሰጠው በኋላ እንዳስፈላጊነቱ ወዴ ኢትዮጵያ ህብረተሰብ ጤና ኢንስቲትዩት ለ ምርመራ የሚሄድ ሲሆን የጥናቱን ዉጤት ለመድገም ወይም ለማረጋገጥ አስፈላጊ ሊሆን ስለሚችል የተሰበሰበዉ የደም ናሙና ለተወሰነ ጊዜ ሊከማች ችላል፡፡

በጥናቱ ያለመሳተፍ ወይም ከጥናቱ የመውጣት መብት

በዚህ ጥናት ዉስጥ መሳተፍ ካልፈለጉ በጥናቱ ያለመሳተፍ ሙሉ መብት አለዎት፡፡ በጥናቱ አለመሳተፍዎ በምንም አይነት መንገድ በዚህ ሆስፒታል ውስጥ በሚያገኙት ህክምና ላይ ምንም ተፅዕኖ አይኖረውም፡፡ ለመሳተፍ ከተስማሙ በኋላ እንኳ ሃሳብዎን ከቀየሩ በማንኛውም ጊዜ ከተሳትፎው መውጣት ይችላሉ፡፡ ይህን በማድረግዎ በህክምናዎም ሆነ በሌላ መልኩ የሚደርስብዎ ችግር የለም፡፡

ተጨማሪ ማብራሪያ ቢፈልጉ

ማንኛውም ከጥናቱ ጋር ተያያዥነት ያላቸው ጥያቄዎች ካሉዎ ወይም ተጨማሪ ማብራሪያ ቢፈልጉ ከአሁን ጀምሮ ወደፊትም

መጠየቅ ይችላሉ፡፡ ወደፊት ጥያቄ መጠየቅ ወይም ማብራሪያ ቢፈልጉ የጥናቱን ተመራማሪዎች እና የአድስ አበባ ዩንቨርስቲ የጤና ሳይንስ ኮሌጅ የጥናት እና ስነ መግባር ኮሚቴ በሚከተለው አድራሻ ማግኘት ይችላሉ፡፡

1. ፋጡማ ሀሰን ፤ ስልክ፤ +251- 911418062
2. ፕ/ር ፍቅሬ እንቁስላሴ ፤ ስልክ፤ +251- 912 45 97 07
3. ፕ/ር እህመድ አሊ ፤ ስልክ፤ +251- 911 68 43 99
4. ዶ/ር አዳሙ አድሴ ፤ ስልክ፤ +251- 911 404954
5. ዶ/ር ግርማ ታየ ፤ ስልክ፤ +251- 911 76 99 26
6. ዶ/ር አስቴር ጸጋየ ፤ ስልክ፤ +251- 911 69 60 85
7. ዶ/ር ማቲወስ አሰፋ ፤ ስልክ፤ +251- 911 24 05 21

የጤና ሳይንስ ኮሌጅ የጥናት እና ስነ መግባር ኮሚቴ ፤ ስልክ፤ +251- 11 8- 96 13 96

ለ. ከጡት ካንሰር ነጻ ለሆኑ ተሳታፊዎች

ዋና አጥኚ፡ ፋጡማ ሀሰን (አአዩ፣ሕክምና ላቦራቶሪ ሳይንስ ት/ት ክፍል)

አማካሪዎች/ሱፐርቫይዘሮች

1. ፕ/ር ፍቅሬ እንቁስላሴ (አአዩ ፣ ህብረተሰብ ጤን ሳይንስ ት/ቤት)
2. ፕ/ር እህመድ አሊ (አአዩ ፣ ህብረተሰብ ጤን ሳይንስ ት/ቤት)
3. ዶ/ር አዳሙ አድሴ (አአዩ ፣ ህብረተሰብ ጤን ሳይንስ ት/ቤት)
4. ዶ/ር ግርማ ታየ (አአዩ ፣ ህብረተሰብ ጤን ሳይንስ ት/ቤት)
5. ዶ/ር አስቴር ጸጋየ (አአዩ፣ሕክምና ላቦራቶሪ ሳይንስ ት/ት ክፍል)
6. ዶ/ር ማቲወስ አሰፋ (አአዩ፣ የካንሰር ሕክምና ክፍል)

ስፖንሰር፡ አዲስ አበባ ዩኒቨርሲቲ (አአዩ)

የጥናቱ ርዕስ፡ በአዲስ አበባ ዩኒቨርሲቲ ጥቁር አንበሳ ሆስፒታል ካንሰር ህክምና ክፍል ለጡት ካንሰር ተጋላጭነትን የሚጨምሩ መንስኤዎች፤ ለሚደረገዉ ህክምና ያላቸዉ ክትትል እና ህክምና ዉጤታቸዉ ምን እንደሚመስልየሚደረግ ጥናት ነዉ::

መግቢያ

ይህ ጥናት አዲስ አበባ ዩኒቨርሲቲ ጥቁር አንበሳ ሆስፒታል የጡት ካንሰር ህሙማን እና ከጡት ካንሰር ነጻ የሆኑ ህሙማን ላይ ሲሆን፤ የጥናቱ አላማ ለጡት ካንሰር ተጋላጭነትን የሚጨምሩ መንስኤዎችን& ህሙማን ለሚደረገዉ ህክምና ያላቸዉ ክትትል እና ህክምና ዉጤታቸዉ ምን እንደሚመስልየሚደረግ ጥናት ነዉ::

አሁን ስለ ጥናቱ አስፈላጊ መረጃዎችን ከሰጠንዎት በኋላ በጥናቱ እንዲሳተፉ ጥሪ ዕናደርጋለን:: በጥናቱ ለመሳተፍ እንደአስፈላጊነቱ ጊዜ ወስደው በማሰብ ወይም ከሌላ ሰው ጋር በመማከር መወሰን ይችላሉ:: በዚህ የስምምነት ቅፅ ውስጥ አዳዲስ ወይም ሙያዊ ቃላት ሊገኙ ይችላሉ:: በመሆኑም ማንኛውም ግልፅ ያለሆነ ሃሳብ ሲያጋጥምዎ ቅፁን የሰጠዎትን ሰው ማበራሪያ መጠየቅ ይችላሉ::

የጥናቱ ዓላማ

በአሁኑ ጊዜ የጡት ካንሰር በተለይ እንደ ኢትዮጵያ ባሉ ታዳጊ አገሮች ውስጥ የተለመደ የጤና ችግር እየሆነ ይገኛል:: ይሁን እንጂ ብዙዎቹ የጡት ካንሰር ታማሚዎች ወዴ ህክምና ተቋማት የሚመጡት በጣም ዘግይተዉ ስለሆነ ለሚታዘዝላቸዉ ህክምና ያላቸዉ ክትትል ፤ የህክምና ዉጤታቸዉ እና ከበሽታዉ ለመዳን ያላቸዉ እድል በጣም አነስተኛ ነዉ:: በዚህ ምርምር ለማጥነት የታቀደዉ ለጡት ካንሰር ተጋላጭነትን የሚጨምሩ መንስኤዎችን& መለየት& ለሚደረገዉ ህክምና ያላቸዉ ክትትል ማየት፤ ህክምና እንዳከታተሉ የሚያግዷቸዉን ሁኔታዎች መለየት እና በህክምና ክትትሉ የሚያገኙትን

ዉጤት ወይም የጤንነት ሁኔታ ለማወቅ ነዉ፡፡ በዚህ ጥናት የሚገኘዉ መረጃ ለወደፊት የጡት ካንሰርን፣ ለመከላከል፣ ታማሚዎች የተሻለ የህክምና ክትትል እንድኖራቸዉ እንድሁም ለጡት ካንሰር የሚያጋልጡ ሁኔታዎችን ለማስወገድ ይረዳል፡፡ የላቦራቶሪዉ ዉጤት ለተሳተፊዎች የሚገለጽ ሳይሆን ለጥናቱ ዓላማ ብቻ ይዉላል፡፡

ጥናቱ የሚካሄድበት መንገድ

ይህን ጥናት ለማድረግ ከጡት ካንሰር ነጻ የሆኑትን ተሳታፊዎች ለመምረጥ በሙያዉ ላይ ልምድ ባለዉ ሀኪም የጡት ምርመራ ይደረጋል፡፡ የጡት ምርመራ ከተደረገ በኋላ ለእያንዳንዱ የጥናት ተሳታፊ የሚሆን መጠይቅ የተዘጋጀ ሲሆን ከጡት ካንሰር ነጻ የሆኑት ተሳታፊዎች ይጠየቃሉ፡፡ በመጨረሻም 5 ሚሊ ሊትር የሚሆን የደም ናሙና ይሰበሰባል፡፡ የደም ናሙናዉ በሰለጠኑ የላቦራቶሪ ባለሙያዎች የሚሰበሰብ ሲሆን ለዚሁ ጉዳይ በተዘጋጁ እና ጽዱ በሆኑ የላቦራቶሪ እቃዎች ሥለሚሰበሰብ ሂደቱ ምንም ጉዳት አያስከትልም፡፡

የተሳታፊዎች አመራረጥ

የዚህ ጥናት ተሳታፊዎች በጥቁር አንበሳ ሆስፒታል ለተመላላሽ ህክምና ለይ ያሉ አዋቂ ሴቶች ሲሆኑ፤ በምርጫዉ ወቅት ሁሉም የጥናቱ ተሳታፊዎች ፈቃደኝነታቸዉን ተጠይቀዉ ይመረጣሉ፡፡

በፈቃደኝነት ላይ የተመሰረተ ተሳትፎ

በዚህ ጥናት ላይ መሳተፍ ሙሉ በሙሉ በርስዎ ፈቃድ ላይ ብቻ የተመሰረተ ይሆናል፡፡ ስለሆነም፣ መሳተፍ አና አለመሳተፍ

የርስዎ ነፃ ምርጫ ነው፡፡ በዚህ ጥናት ላይ ቢሳተፉም ባይሳተፉም፣ በዚህ የህክምና ተቋም የሚሰጠውን ህክምና ካለልዩነት

ያገኛሉ፡፡

የጥናቱ ዘዴዎችና ሂደቶች

በዚህ ጥናት ለመሳተፍ ፈቃደኛ ከሆኑ፣ ከላይ በተጠቀሰው መሰረት የጡት ምርመራ ይደረጋል፡፡ የጡት ምርመራ ተደርጎላቸዉ ዉጤታቸዉ ነጻ ከሆነ በተዘጋጁት መጠይቆች መረጃ ይሰበሰባል፡፡ በተጨማሪም ክብደተዎ እና ቁመተዎ ይለካል፡፡ በመጨረሻም 5 ሚሊ ሊትር የሚሆን የደም ናሙና ይሰበሰባል፡፡ የደም ናሙናዉ የሚሰበሰበዉ በታሸጉ እና ፍጹም ንጽህናቸዉን በጠበቁ መርፌዎች እና ሲሪንጆች ነዉ፡፡ የደም አወሳሰድ ሂደቱ ቀላል እና ህመም የልለዉ ነዉ:: ባጠቃላይ ጠቃሚ መረጃዎችን ለማጠናቀር ዕና የደም ናሙናዉን ለመሰብሰብ ከ30 እስከ 45 ደቂቃ ሊወስድ ይችላል፡፡ በጥናቱ ተሳታፊ በመሆንዎ ምክንያት ብቻ ለተጨማሪ ቀጠሮ እንዲመጡ አይጠየቁም፡፡

ጉዳት

በዚህ ጥናት መሳተፍ ከመደበኛው የህክምና ሂደት የተለየ ምንም አይነት የተሳታፊዎችን ደህንነት ሊጎዳ የሚችል ተጨማሪ

ሂደት እይካሄድም፡፡ በጥናቱ በመሳተፍዎ ምክንያት የሚደርስብዎ አደጋ ወይም መንገላታት የለም፡፡ ስለሆነም በጥናቱ

መሳተፍ የሚስከተለው ጉዳት የለም፡፡

ጥቅም

በዚህ ጥናት መሳተፍ የሚያስገኘዉ ቀጥተኛ የግል ጥቅም ጡታቸዉ ላይ እባጭ ያለባቸዉ ሴቶች ወዴ ተሻለ ምርመራ እና ህክምና የሚሄዱበት መንገድ ይመቻቻል፡፡ በተጨማሪም እርስዎ በዚህ ጥናት መሳተፍዎ ጥናቱ ያነሳቸውን

ጥያቄዎች በመመለስ /በማገዝ ለወደፊት የሕብረተሰቡን በተለይም የሴቶችን ጤና ለመሻሻል ከፍተኛ አስተዋፅዖ ያደርጋል፡፡ ይህን በማድረገዎ የጡት ካንሰርን ለመቆጣጠር እና ለመከላከል በሚደረግ ጥረት የበኩለዎን አስተዋፅዖ የደርጋሉ፡፡

ምስጢራዊነት

ማናቸውም የጤናና ሌሎች በጥናቱ ምክንያት የሚገኙ እርስዎን የሚመለከቱ መረጃዎች በከፍተኛ ምስጢርነት የሚጠበቁ

ሆኖ በእርስዎ ፈቃድና ህግ በሚያዘው መሠረት ካልሆነ በስተቀር ለሌላ ወገን አይገለፁም፡፡ ስለ እርስዎ የተሰበሰበ መረጃ

በሙሉ በይለፍ ቃል በሚዘጋ የመረጃ ቋት ውስጥ የሚከማች ሲሆን፣ መረጃዎቹ ከጥናት ቡድኑ እጅ በሚወጡበት ጊዜ

የማንነት መገለጫዎች በሙሉ ለሌላ ሰው በማይታወቁ የምስጢር ኮድ ይቀየራሉ፡፡

የዚህ ጥናት ውጤት በህትመት ውጤቶች ላይ የሚወጣ ቢሆን ወይም በተለያዩ መንገዶች ለህዝብ የሚቀርብ ቢሆን የርስዎ

ስም ወይም ማንነት በምንም አይነት መንገድ አይገለፅም፡፡

ናሙና ስለማከማቸት እና ስለማዘዋወር

የተሰበሰበው ናሙና ምስጢራዊ መለያ ከተሰጠው በኋላ እንዳስፈላጊነቱ ወዴ ኢትዮጵያ ህብረተሰብ ጤና ኢንስቲትዩት ለ ምርመራ የሚሄድ ሲሆን የጥናቱን ዉጤት ለመድገም ወይም ለማረጋገጥ አስፈላጊ ሊሆን ስለሚችል የተሰበሰበዉ የደም ናሙና ለተወሰነ ጊዜ ሊከማች ችላል፡፤

በጥናቱ ያለመሳተፍ ወይም ከጥናቱ የመውጣት መብት

በዚህ ጥናት ዉስጥ መሳተፍ ካልፈለጉ በጥናቱ ያለመሳተፍ ሙሉ መብት አለዎት፡፡ በጥናቱ አለመሳተፍዎ በምንም አይነት መንገድ በዚህ ሆስፒታል ውስጥ በሚያገኙት ህክምና ላይ ምንም ተፅዕኖ አይኖረውም፡፡ ለመሳተፍ ከተስማሙ በኋላ እንኳ ሃሳብዎን ከቀየሩ በማንኛውም ጊዜ ከተሳተፎው መውጣት ይችላሉ፡፡ ይህን በማድረግዎ በህክምናዎም ሆነ በሌላ መልኩ የሚደርስብዎ ችግር የለም፡፡

ተጨማሪ ማብራሪያ ቢፈልጉ

ማንኛውም ከጥናቱ ጋር ተያያዥነት ያላቸው ጥያቄዎች ካሉዎ ወይም ተጨማሪ ማብራሪያ ቢፈልጉ ከአሁን ጀምሮ ወደፊትም

መጠየቅ ይችላሉ፡፡ ወደፊት ጥያቄ መጠየቅ ወይም ማብራሪያ ቢፈልጉ የጥናቱን ተመራማሪዎች እና የአድስ አበባ ዩንቨርስቲ የጤና ሳይንስ ኮሌጅ የጥናት እና ስነ መግባር ኮሚቴ በሚከተለው አድራሻ ማግኘት ይችላሉ፡፡

1. ፋጡማ ሀሰን ፤ ስልክ፤ +251- 911418062
2. ፕ/ር ፍቅሬ እንቁስላሴ ፤ ስልክ፤ +251- 912 45 97 07
3. ፕ/ር እህመድ አሊ ፤ ስልክ፤ +251- 911 68 43 99
4. ዶ/ር አዳሙ አድሴ ፤ ስልክ፤ +251- 911 404954
5. ዶ/ር ግርማ ታየ ፤ ስልክ፤ +251- 911 76 99 26
6. ዶ/ር አስቴር ጸጋየ ፤ ስልክ፤ +251- 911 69 60 85
7. ዶ/ር ማቲወስ አሰፋ ፤ ስልክ፤ +251- 911 24 05 21

የጤና ሳይንስ ኮሌጅ የጥናት እና ስነ መግባር ኮሚቴ ስልክ +251- 11 8- 96 13 96

Annex V: Certificate of Consent (in Amharic)

የስምምነት ውል

ማንበብና መፃፍ ለሚችሉ ተሳታፊዎች

ከላይ በዝርዝር የተመለከተውን መረጃ አንብቤ ወይም ተነቦልኝ በሚገባ ተረድቻለሁ፡፡ ጥያቄ የመጠየቅ እድልም አግኝቼ ጥያቄዎቼ በተገቢ ሁኔታ ተመልሰውልኛል፡፡ ስለጥናቱ የተሰጠኝን መረጃ በትክክል ተረድቼ በጥናቱ ለመሳተፍ በፈቃደኝነት ተስማምቻለሁ፡፡

የተሳታፊዋ፡ስም_____ፊርማ_____ቀን_____

ማንበብና መፃፍ ለማይችሉ ተሳታፊዎች

ስምምነቱ ማንበብና መፃፍ በምትችል (በሚችል) ምስክር አማካኝነት ይፈረማል፡፡ ከተቻለ ምስክሮች በተሳታፊዎች ቢመረጡ ወይም ከጥናት ቡድኑ ጋር ግንኙነት ባይኖራቸው ይመረጣል፡፡ ማንበብና መፃፍ የማይችሉ ተሳታፊዎች በጣታቸው አሻራ ይፈርማሉ፡፡ ምስክሮችም መረጃውን በትክክል ለተሳታፊዋ ስለማንበባቸው ይፈርማሉ፡፡ በስምምነት ቅፁ ላይ የተዘረዘረውን መረጃ ለታካሚዋ በትክክል ማንበቤን እንዲሁም ታካሚዋ ግልፅ ያልሆኑላቸውን ነጥቦች የመጠየቅ ዕድል አግኝተው ጠይቀው መረዳታቸውን እመሰክራለሁ፡፡ በተጨማሪም ታካሚዋ በጥናቱ ለመሳተፍ የተስማሙት በነፃ ፈቃዳቸው መሆኑን እመሰክራለሁ፡፡

የምስክር ስም_____ የታካሚ/ተሳታፊ ጣት አሻራ

የምስክር ፊረማ_____ቀን _____

የአጥኚ ወይም የውል ተቀባይ ቃል

ለታካሚዋ/ተሳታፊዋ ስለጥናቱ የሚቻለውን ያህል በቂ መረጃ ሰጥቻለሁ፡፡ በተቻለ መጠንም ታካሚዋ ስለጥናቱ፣ አላማ አንዲሁም ጥናቱ ስለሚካሄድባቸው ዘዴዎችና በጥናቱ ወቅት ስለሚከናወኑ ድርጊቶች መረዳታቸውን አረጋግጫለሁ፡፡

ታካሚዋ/ተሳታፊዋ ስለጥናቱ ጥያቄ የመጠየቅ ዕድል ተሰጥቷቸው የጠየቋቸውን ጥያቄዎች ባለኝ ዕውቀት መጠን በትክክል አብራርቼ መልሻለሁ፡፡

ተሳታፊዋን ካለምንም ማስገደድ በነፃ ፈቃዳቸው በጥናቱ ለመሳተፍ መስማማታቸውን አረጋግጣለሁ፡፡

የዚህ ስምምነት ውል ቅጂ ለተሳታፊዋ ተሰጥቷል፡፡

የአጥኚ ወይም ውል ተቀባይ ስም_____ፊርማ_____ቀን_____

Annex VI : Data Collection Instrument Questionnaire (Amharic version)

የጥናቱ/ የምርምሩ መጠየቂያ ቅፅ

ለጡት ካንሰር ተጋላጭለትን የሚጨምሩ መንስኤዎችን ለመለካት የሚረዱ ጥያቄዎች

1. አጠቃላይ መረጃ

1.1 የጥናቱ ተሳታፊ መለያ_____

1.2 መረጃዉ የተሰበሰበበት ቀን_____

1.3 መረጃዉ የተሰበሰበበት ቦታ_____

1.4ካርድ ቁጥር_____

1.5. ስልክ ቁጥር_____

የጥናቱ/ የምርምሩ መጠየቂያ ቅፅ፤ ለጡት ካንሰር ተጋላጭለትን የሚጨምሩ መንስኤዎችን ለመለካት የሚረዱ ጥያቄዎች

ተ.ቁ	ጥያቄ	ምላሽ
100	**ማህበራዊ ጉዳዮችን እና የስነ- ህዝብ መረጃ የሚመለከቱ ጥያቄዎች**	
101	እድሜሽ ስንት ነው ?	
102	ሀይማኖት	1. ኦርቶዶክስ 2. ሙስሊም 3. ፕሮቴስታንት 4. ሌላ ካለ ይገለጽ_____
103	ብሄረሰብ	1. አሮሞ 2. አማራ 3. ትግሬ 4. ሌላ ካለ ይገለጽ_____
104	የጋብቻ ሁኔታ	1. ያገባች 2. ያላገባች 3. የፈታች 4. የትዳር አጋር የሞተባት 5. ሌላ ካለ ይገለጽ _____
105	የትምህርት ደረጃ	1. ያልተማረች 2. ማንበብ እና መጻፍ 3. የመጀመሪያ ደረጃ (1-8) 4. ሁለተኛ ደረጃ (9-12) 5. ሦስተኛ ደረጃ (ዲፕሎማ/ ዲግሪ) እና ከዛ በላይ 6. ሌላ ካለ ይገለጽ_____
106	ያገቡ ከሆነ የባለቤተዎ የትምህርት ደረጃ	1. ያልተማረ 2. ማንበብ እና መጻፍ 3. የመጀመሪያ ደረጃ (1-8)

		4. ሁለተኛ ደረጃ (9-12) 5. ሦስተኛ ደረጃ (ዲፕልማ/ ዲግሪ) እና ከዛ በላይ 6. ሌላ ካለ ይገለጽ_____
107	የስራ ሁኔታ	1 ግብርና 2. የቤት እመቤት 3. ተማሪ 4. ነጋዴ 5. የመንግስት ሠራተኛ 6.ሌላ ካለ ይገለጽ_____
108	የመኖሪያ ቦታ	1 ከተማ 2. ገጠር ክልል_____ ዞን _____ ወረዳ_____
109	የመኖሪያ ቦታ ከአድስ አበባ ዉጭ ከሆነ ርቀቱ ምን ያህል ነዉ	_____ኪ.ሜ
110	የቤተሰቡ ወርሀዊ ገቢ ምን ያህል ነው?	_____የኢትዮጵያ ብር
111	የሚኖሩበት ቤት የእርሰዎ ነው የኪራይ?	ነ. የእራሴ 2. የኪራይ
200	ከፍል ሁለት፡ ከመራቢያ/ወሊድ እና ከሰዉነት ከሚመነጩ ቅመሞች ጋር የተያያዙ ጥያቄዎች	
201	ያገቡ ከሆነ የመጀመሪያ ባለዎትን በስንት ዓመተዎ አገቡ?	_____ዓመት
202	አርግዘው ያውቁ ነበር?	1 አዎ 2. የለም/አላዉቅም → ወደ ጥያቄ 210 ይሂዱ
203	መልሱ አዎ ከሆነ በሂዎት ያለ ልጅ ወልደው ያውቁ ነበር?	1. አዎ 2. አላዉቅም
204	መልሱ አዎ ከሆነ ስንት ልጆች አሉዎት ?	_____
205	የመጀመሪያ ልጆዎትን ሲዎለዱ ስንት ዓመተዎ ነበር?	ነ. እድሜ _____ 2. አላዉቅም
206	ልጆዎትን አጥብተዉ ያዉቃሉ?	1. አዎ 2. አላዉቅም
207	መልሰዎ አዎከሆነ ባጠቃላይለምን ያህል ጊዜ ጡት አጠቡ ?	_____
208	ዉርጃ ገጥሞዎት ያዉቃል?	1. አዎ 2. አያዉቅም
209	መልሰዎ አዎ ከሆነ ምን ያህል ጊዜ ገጠመወት ?	_____የዉረጃ ብዛት
210	ለመጀመሪያ ገዜ የወር አበባ ያዩት በስንት አመተዎ ነበር?	1. ዕድሜ_____ 2. የወር አበባ አላየሁም 3. አላቀዉም/አላስታዉስም
211	ባሁኑ ጊዜ የወር አበባዎት ቆሟል?	1. አዎ 2. አልቆመም 3. የወር አበባ አላየሁም
212	መልሰዎ አዎ ከሆነበ ስንት አመተዎ ነዉ የቆመዉ?	1. የቆመበት ዕድሜ_____ 2. አላቀዉም/አላስታዉስም

213	የወር አበባዎት የቆመዉ በምን ምክንያት ነበር?	1. በተፈጥሮ/በማረጥ 2. በቀዶ ህክምና ምክንያት 3. ሌላ ካለ ይገለጽ_____
214	ከጡትዎ ላይካንሰር ያልሆነ እባጭ ለማስወገድ ቀዶ ህክምና አድርገዉ ያዉቃሉ?	1. አዎ 2. አላደረግኩም → ወደ ጥያቄ 216 ይሂዱ
215	መልሰዎ አዎ ከሆነ ባጠቃላይ ጡትዎ ላይ ስንትጊዜ በቀዶ ህክምና አድርገዋል?	1. ያደረጉት ቀዶጥገና ብዛት_____ 2. አላቀዉም/አላስታዉስም
216	መልሰዎ አዎከሆነ ይህን የመጀመሪያ በቀዶ ህክምና ሲያደርጉ ስንት ዓመተዎ ነበር?	1.በቀዶጥገና ያደረጉበ ትዕድሜ_____ 2.አላቀዉም/አላስታዉስም
217	ኪኒን ወይም ሆርሞን ያላቸዉ የወሊድ መቆጣጠሪያ ተጠቅመዉ ያዉቃሉ?	1. አዎ 2. ተጠቅሜ አላዉቅም → ወደ ጥያቄ 300 ይሂዱ
218	መልሰዎ አዎ ከሆነ የወሊድ መቆጣጠሪያ ኪኒኑንሲጀምሩስንት ዓመተዎነበር?	1. ኪኒኑን የጀመሩበት ዕድሜ_____ 2. አላቀዉም/አላስታዉስም
219	ባሁኑ ጊዜ ኪኒን ወይም ሆርሞን ያላቸዉየወሊድ መቆጣጠሪያ እየተጠሙ ነዉ?	1. አዎ 2. አልጠቀምም
220	መልሰዎ ባሁኑ ጊዜ አልጠቀምም ከሆነ ለመጨረሻ ጊዜ ኪኒንወይም ሆርሞን ያላቸዉ የወሊድ መቆጣጠሪያ መጠቀም ያቆሙት መቸ ነዉ?	_____ዓመት
221	ባጠቃላይየወሊድ መቆጣጠሪያኪኒን ወይም ሆርሞን ያላቸዉ የወሊድ መቆጣጠሪ ያለምን ያህል ጊዜ ተጠቀሙ?	1. ወር _____ 2. ዓመት_____ 3. አላስታዉስም
222	የመጨረሻ ልጀዎን በስንት ዓመተዎ ነው የወለዱት?	_____ ዓመት
300	ከሆርሞን ጋር የተያያዙ ጥያቄዎች	
301	እርጅናን ለመቀነስ ፕሮጀስትሮን /ኢስትሮጅን ወይም ሌሎች የሴት ሆርሞኖች ተጠቅመዉ ያዉቃሉ? (ይህ ሆረሞን በኪኒን፡ በመርፌ የሚሰጥ ሊሆን ይችላል በማህጸን የሚግቡትን አይጨምርም	ı. አዎ 2. አላዉቅም → ወደ ጥያቄ 400 ይሂዱ
302	መልሰዎ አዎ ከሆነ የሴት ሆርሞኖቹን ለመጀመሪያ ጊዜ የ ተጠቀሙት በስንት ዓመተዎ ነበር?	_____ዓመት

303	ባሁኑ ጊዜ እነዚህን የሴት ሆርሞኖች እየተጠሙ ነዉ?	1. አዎ 2. አልጠቀምም
304	መልሰዎ አልጠቀምም ከሆነ የሴት ሆርሞኖቹን መጠቀም ያቆሙት በስንት ዓመተዎ ነበር?	_____ዓመት
305	መልሰዎ አልጠቀምም ከሆነ የሴት ሆርሞኖቹን መጠቀም ያቆሙት በምን ምክንያት ነበር?	
306	ባጠቃላይ የሴት ሆርሞኖቹን ለምንያህል ጊዜ ተጠቅመዋል?	
307	ሲጠቀሙት የነበረዉ የትኞቹን የሴት ሆርሞኖች ነበር?	ፕሮጀስተሮን ብቻ 2. ኢስትሮጅን ብቻ 3. ሁለቱንም 4. አላዉቀዉም 4. ሌላ ካለ ይገለጽ_____
400	**በቤተሰብ ዉስጥ የጡት ካንሰር ታሪክ የሚመለከቱ ጥያቄዎች** **ጥያቄ ቁጥር 401 ላይ የሚመለከተዉ የተፈጥሮ እናት እና አባትን ብቻ ነዉ፤፤ የንጀራ እናትን እና የእንጀራ አባትን ወይም የጉድፈቻ ቤተሰብን አይጨምርም**	
401	እናት፡ የጡት ካንሰር_____ የእንቁላል ማምረቻ ካንሰር_____ የጡት ካንሰር የታከሙበት እድሜ፡ _____ እህት፡ የጡት ካንሰር_____የእንቁላል ማምረቻ ካንሰር_____ የጡት ካንሰር የታከሙበት እድሜ፡ _____ አያት፡ የጡት ካንሰር_____የእንቁላል ማምረቻ ካንሰር_____ የጡት ካንሰር የታከሙበት እድሜ፡ _____ አባት፡ የጡት ካንሰር_____ የፕሮስቴት ካንሰር_____ የጡት ካንሰር የታከሙበት እድሜ፡_____ ሌላ፡_____ የጡት ካንሰር_____የእንቁላል ማምረቻ ካንሰር_____ የጡት ካንሰር የታከሙበት እድሜ፡_____	
500	**ከባህሪ እና ከአኗኗር ዘዴ ጋር የተያያዙ ጥያቄዎች**	
501	በተደጋጋሚ ለምሳሌ ቢያንስ በቀን አንድ ሲጋራለ3 ወር ወይም ከዛ በላይ አጭሰዉ ያዉቃሉ?	1. አዎ 2. አላዉቅም → ወደ ጥያቄ 507 ይሂዱ
502	መልሰዎ አዎ ከሆነ ሲጋራ ማጨስ የጀመሩት በስንት ዓመተዎ ነበር?	_____ዓመት
503	መልሰዎ አዎ ከሆነ አሁንም አዘዉትረዉ ሲጋራ ያጨሳሉ?	1. አዎ 2. አላጨስም
504	መልሰዎ አላጨስም ከሆነ ሲጋራ ማጨስ ያቆሙት በስንት ዓመተዎ ነበር?	_____ዓመት
505	ቢያንስ በቀን አንድ ሲጋራ ለምን ያህል ወራት ወይም ዓመታት አጭሰዋል?	_____ወራት _____ዓመት
506	አብዝሀኛዉን ጊዜ በቀን ምን ያህል ሲጋራ ያጨሳሉ?	_____.በቀን የሚያጨሱት ብዛት
507	በሚኖሩበት ቤት/ክፍልዉስጥ ሲጋራየሚያጨስ ሰዉ ነበር/አለ?	1. አዎ 2. የለም → ወደ ጥያቄ 509 ይሂዱ

508	መልሰዎ አዎ ከሆነ በሚኖሩበት ቤት/ክፍልዉስጥ ለምንያህልጊዜ አጨሱ?	ወር_____ዓመት_____.
509	ምግብ ለማብሰል የሚጠሙት በምንድን ነዉ?	ı. በእንጨት/የከብት እበት 2. በኤሌክትሪክ 3. በከሰል 4. በቡታጋዝ 5. ሌላ ካለ ይገለጽ_____
510	ምግብ ለማብሰል የሚጠቀሙበት የብቻ ክፍል አለዎት ወይ?	ı. አዎ 2. የለኝም
511	አልኮል ለምሳሌ ጠላ፤ አረቄ፤ ጠጅ ;ቢራ፤ ወይም ውስኪ አዘውትረው ለምሳሌ ቢያንስ በሳምንት አንድ ቀን ለ6 ወር ወይም ከዛ በላይጠጥተዉ ያዉቃሉ?	1. አዎ 2. አላዉቅም→ ወደ ጥያቄ 600 ይሂዱ
512	መልሰዎ አዎ ከሆነ ቢያንስ በሳምንት አንድ ቀን ለ6 ወር ወይም ከዛ በላይመጠጣት የጀመሩት በስንት ዓመተዎ ነበር?	1. አዎ 2. አልጠጣም
513	መልሰዎ አዎ ከሆነ አሁንም ቢያንስ በሳምንት አንድ ቀን ይጠጣሉ?	1. አዎ 2. አልጠጣም
514	መልሰዎ አልጠጣም ከሆነ አልኮል መጠጣት ያቆሙት በስንት ዓመተዎ ነበር?	_____ዓመት
515	ለምን ያህል ወራት ወይም ዓመታት ቢያንስ በሳምንት አንድ ቀን አልኮል ጠጡ?	
516	አብዛሃኛዉን ጊዜ በሳምንት ምን ያህል ጠርሙስ ወይም ብርጭቆ አልኮል ይጠጣሉ?	_____ብርጭቆ_____ጠርሙስ
600	ከአመጋገብ እና ከሰዉነት እንቅስቃሴ ጋርየተያያዙ ጥያቄዎች	

የሚከተሉትን የምግብ አይነቶች ምን ያህል አዘዉትረዉ ይመገባሉ? ከጥያቄዎቹ ፊተለፊት ይህን ምልክት (“√ “) ያስቀምጡ

ተ.ቁ	የምግብ ዓይነት	ሀ አንድ ጊዜ/በቀን	ለ ከአንድ ጊዜ በላይ/በቀን	ሐ 2-3 ጊዜ/በሳምንት	መ አልፎ አልፎ (ለምሳሌ በበዓል ቀን ፤ ልዩ ቀን)	ሠ በጭራሽ/ አልመገብም
601	አትክልት (ቲማቲመ፤ ጎመን ወ.ዘ.ተ)					
602	ፍራፍሬ (ብርቱካን፤ ሙዝ ወ.ዘ.ተ)					
603	ስጋ (የዶሮ፤ የዓሳ፤ የበግ፤ የበሬ ወ.ዘ.ተ)					
604	ወተት እና የወተት ተዋጽኦ (ቅቤ፤ እርጎ፤ አይብ ወ.ዘ.ተ)					

605	የረጋ ዘይት አጠቃቀመዎ እንደት ነው?	1. አልጠቀምም 2. ሁልጊዜ እጠቀማለሁ 3. አንዳንድ ጊዜ እጠቀማለሁ
606	አድካሚ የሆነ የሰዉነት እንቅስቃሴ (ለምሳሌ ዋና፤ ሩጫ፤ ቅርጫት ኳስ፤ ሳይክል መንዳት)ያደርጋሉ?	1. አዎ 2. አላደርግም
607	መልሰዎ አዎ ከሆነ በአማካይ በቀን ስንት ስዓት ይሰራሉ/ያደርጋሉ?	_____ስዓት/በቀን
608	ቀለል ያለ የሰዉነት እንቅስቃሴ (ለምሳሌ እርምጃ፤ ቴኒስ፤ ወ.ዘ.ተ) ያደርጋሉ?	1. አዎ 2. አላደርግም
609	መልሰዎ አዎ ከሆነ በአማካይ በቀን ስንት ስዓት ይሰራሉ/ያደርጋሉ?	_____ስዓት/በቀን
700	ከጨረር ጋር የተያያዙ ጥያቄዎች	
701	ደረተዎ አካባቢ ራጅ ተነስተዉ ያዉቃሉ?	1. አዎ 2. አላውቅም
702	መልሰዎ አዎ ከሆነ	

	የተነሱት ራጅ ብዛት	መጀመሪያ ራጅ የተነሱበት ዕድሜ
703. የልብ ራጅ		
704. ሌላ ካለ ይግለጹ		

800	የቁመት፤ ክብደት እና የላቦራቶሪ ውጤቶች	
801	ቁመት	_____ሜ
802	ክብደት	_____ኪ.ግ
900	**የላቦራቶሪ ዉጤት**	
901	የደምዓይነት	ኤቢኦ (ABO _____ አር ኤች (Rh)_____
902	ሄሞግሎቢን	_____ግ.ም/ደ.ሊ
903	ሄማቶክሪት	_____%
804	ነጭየደምሴልብዛት	_____ሚ.ሜ^3
905	ቀይየደምሴልብዛት	_____ሚ.ሜ^3
906	የፕላትሌትብዛት	_____ሚ.ሜ^3

የሚቀጥለዉ የቀጠር ቀን _____

መጠይቁ የተሞላበት ቀን፡_____የመረጃ ሰብሳቢዉስም፡_____ፊርማ፡_____ስለ ትብብረዎ እጅግ በጣም አመሰግናለሁ፡፡

Annex VII: Principles materials and procedures for laboratory tests

1. **Principle and reagents of Sysmex hematology analyzer:**

The Sysmex KX-21N is a quantitative automated hematology analyzer for in vitro diagnostic use for determining 17 hematological parameters. Examination of the numerical and/or morphologic findings of the complete blood count are useful in diagnosis of such disease states as anemias, leukemias, allergic reactions, viral, bacterial, and parasitic infections. The Sysmex KX-21N analyzer directly measures the WBC, RBC, HGB, HCT, PLT, LYM#, MIXED# and NEUT#. The remaining parameters are calculated or derived, MCV, MCH, MCHC, MPV, RDW-CV and RDW-SD, and differential percentages LYM%, MIXED%, NEUT%.

The KX-21N counts and sizes red blood cells (RBC) and platelets (PLT) using electronic resistance detection. Hematocrit (HCT) is measured as the ratio of the total RBC volume to whole blood using cumulative pulse height detection. Hemoglobin (HGB) is converted to methemoglobin, and read photometrically at 555 nm.

White blood cells (WBC) are analyzed by direct current and discriminated into a three-part differential using Particle Distribution Analysis (PDA). The resulting WBC histogram is discriminated into lymphocyte, neutrophil and mixed cell populations. The mixed cell population contains monocytes, basophils and eosinophils [117].

SPECIMEN:

1. Required specimen: Whole blood anticoagulated with EDTA preferred.

2. Specimen volumes required: Optimal draw is a tube drawn to capacity. The collection tube should be filled to a minimum of one-half full for acceptable results. An EDTA micro-container filled above the 250 uL line is adequate for testing in the whole blood mode.

3. Unacceptable specimens including those listed below must be redrawn:

a. Clotted samples or those containing clots, fibrin strands, or platelet clumps. All specimens will be checked visually for obvious clots prior to sampling by the analyzer.

b. Check capillary tubes manually with a toothpick for clots.

c. Grossly hemolyzed samples.

d. Samples drawn above an IV.

4. Characteristics that may affect test results are: lipemia, icterus, and cold agglutinins

5. Stored Specimen Stability

a. If stored at 4oC within 6 hours of collection, EDTA blood samples with normal results may be analyzed up to 48 hours without significant loss of differential stability.

b. Sample stability at room temperature is 8 hours. Samples stored at room temperature may exhibit an increase in MCV, and HCT, and a decrease in MCHC after 16 hours. These changes may be minimized by refrigeration.

c. Capillary tubes are stable 4 hours when stored at 2-8oC (warm and remix before analyzing).

d. Allow refrigerated samples to come to room temperature for 30 minutes then mix by hand inversion before analysis.

6. Do not place samples on a mechanical rocker. Constant rocking may cause PLT clumping and alter white cell membranes resulting in inappropriate flagging.

WARNING: All patient specimens should be considered potentially infectious and must be handled with precautions used for human blood, as described in CDC recommendations and in compliance with the Federal OSHA Bloodborne Pathogen Standard, 29 CFR part 1910.1030. Follow specimen handling as outlined by laboratory safety policy.

Recommended: Wear gloves, lab coat and safety glasses.

REAGENTS / MATERIALS:

Supplies

1. Deionized water

2. Lint-free, plastic lined lab wipes

3. "filler" pipette supplied with the unit or a 5 cc Syringe.

4. Clorox Ultra bleach (Use when Cellclean is indicated)

5. Sysmex reagents

6. Tri-level commercial controls, Eightcheck-3WP X-TRA

7. Sysmex SCS-1000 whole blood calibrator.

8. To ensure that the new reagent is completely cycled into the system, cycle the KX-21N analyzer 10 times before running controls and/or patients.

9. Run 2 levels of commercial QC to monitor reagent performance. Document QC "OK" on reagent log.

2. Principle of ABO and RH blood grouping

The determination of an ABO blood group is defined by demonstrating the presence or absence of antigens A and/or B on the surface of human red blood cells and by detecting the presence or absence of anti-A and/or anti-B antibodies in the plasma. It is therefore appropriate to identify the erythrocyte antigens using known anti-A and anti-B, then to confirm the results by verifying the presence of the corresponding antibodies in the plasma from the test blood using known red blood cells A_1 and B (reverse group). After the A and B antigens of the ABO blood group system, D is the most important blood group antigen in routine blood banking. Unlike antibodies of the ABO system, those of the Rh system do not occur naturally in the serum, but are most often the result of exposure to the antigen during pregnancy or through transfusion. The presence or absence of the D antigen is determined by testing the red blood cells with Anti-D. Agglutination indicates that the test cells are D positive. No agglutination indicates that the test cells are D negative [118].

Materials and procedures of ABO/Rh blood typing (Slide Method)

Materials

- Whole Blood
- Anti – A antiserum, Anti – B antiserum, Anti-D (Rh) antiserum
- Plastic Pipette
- Rh View Box
- Applicator sticks
- Blood Typing slide
- Work mat/paper towel
- Laboratory Coat
- Disinfecting Wipes
- Biohazard Containers

Procedures

Mix antiserum

7. Place a drop of anti- A, B, and D (Rh) in the labeled wells on the blood typing slide.
8. Mix blood well, and place a small drop of blood in each well.
9. Mix the “a” well with an applicator stick. Mix the “b” well with another applicator stick.
10. Rotate typing slide for two minutes and interpret ABO blood type.
11. Place slide vertically on the Rh view box, rock slide back and forth on the view box for one minute, then interpret Rh data.
12. Replace and dispose of all supplies and equipment according to instruction.
13. Disinfect top and bottom work area, test tube rack, and any other item that may be contaminated with body fluids.

Annex: VIII. Declaration

I the under signed, declared that this is my original work and has never been presented in this or any other any other university, and that all the sources and materials used for this dissertation , have been fully acknowledged.

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Date of examination: July 21/2023

This dissertation has been submitted for examination with my approval as University supervisor.

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Original Article

Socio-demographic and Haematological Determinants of Breast Cancer in a Tertiary Health Care and Teaching Hospital in Addis Ababa, Ethiopia

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Abstract

Background: Breast cancer is the major cause of cancer deaths among women globally. Socio-demographic and haematological characteristics are among the determinants of breast cancer, and these characteristics are supposed to be monitored during early diagnosis and treatment of cases.

Objective: The objective of this study was to assess socio-demographic and haematological profile of patients with breast cancer at Tikur Anbessa Specialized Hospital.

Methods: Case controlled study was conducted among 230 cases and 230 controls from May 2018 to June 2019. Descriptive analysis was made to assess socio-demographic characteristics and independent sample t- test was performed to compare the mean haematological parameters.

Results: The mean age was 42.8 $\pm$ 12.1 years and 39.3 $\pm$ 11.1 years for cases and controls, respectively. About 43.5% of the cases and 14.8% of the controls were not able to read and write. About 76.1% of the cases and 67.4% of the controls were married. The mean values of Haemoglobin, Red Blood cell, Packed Cell Volume for the cases were 13.1 $\pm$ 1.6g/dl; 4.6 $\pm$ 0.54x10^{12}/L; and 38.7 $\pm$ 4.5 %, respectively. These were significantly lower than those of the controls (14.0 $\pm$ 1.3g/dl, 4.8 $\pm$ 0.47 x 10^{12}/L, 40.5 $\pm$ 3.5%, respectively). Mean platelet count was higher among the cases, whereas total White Blood cell count was almost similar.

Conclusion and recommendations: Majority of the cases were less than 40 years of age and were not able to read and write. Most of the RBC parameters of cases were significantly lower than the controls. Therefore, attention should be given for exposed groups and those with the designated haematological abnormalities. [*Ethiop. J. Health Dev.* 2020; 35(2):000-000]

Keywords: Breast cancer, Haematological parameters, Socio-demographic factors, Ethiopia

Background

Breast cancer is the major cause of cancer deaths in women [1]. Though significant progress has been made in breast cancer prognosis and survival, the disease is still the main cause of death among women in low- and middle-income countries [1-3]. There is increase in magnitude of cancer in many African countries, but cancer controlling programs are still extremely low [4].

Socio-demographic factors are linked with breast cancer. According to findings from European countries including Sweden and Norway, higher socioeconomic status of women was significantly associated with breast cancer incidence [5]. Age, marital status, employment status, as well as educational status were determinants of breast cancer incidence as demonstrated by other studies from Iraq [6,7].

Age, marital status, employment status, as well as low educational status were determinants of breast cancer incidence as demonstrated by other studies from Iraq [6-7]. A WHO survey conducted in low-income countries found that country health spending, health care access, rural residence and socioeconomic status were significant factors for cancer screening [8]. In Nigeria, socio-demographic factors increased the risk of late presentation [9].

Breast cancer is the leading cause of morbidity and mortality in Ethiopia, too, gaining conducive opportunities due to long patient delay and advanced stage at diagnosis [10] Trend of breast cancer is increasing, and it is the most predominant type of cancer in Ethiopia [11, 12]. In general, cancer contributes for 5.8% of the total national mortality [13]. It is also found that breast cancer is highly posing a significant public health problem in Ethiopia [14]. On the other hand, most cancer patients have poor awareness. As a result, majority of patients seek treatment at advanced and incurable stage of the disease [15].

Haematological abnormalities are common features to be considered in breast cancer patients. Those parameters could be used as one of the important biochemical tools in the diagnosis of other co-morbidities and treatment monitoring in breast cancer patients [16]. Studies indicate haematological parameters as important investigations that are useful prognostic factors for evaluating the accuracy of risk stratification in breast cancer patients [17, 18]. Studies done in Nigeria showed that most of the haematological parameters were significantly lower among breast cancer patients than among controls [18, 19]. Hematologic parameters were also significantly lower in patients in Iraq [20]. A study in Malaysia revealed that 22% of breast cancer patients had significantly decreased haemoglobin value [21].

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Studies in Ethiopia indicated that, at the time of diagnosis, 80–90% of patients suffer from advanced and incurable cancers [15, 22-24]. Socio-demographic factors may have influence on late presentation and contribute to neglecting sign and symptoms, illnesses, as well as late notifications and treatment delay [9]. Since breast cancer is associated with lifestyle, it is important to investigate and recognise various socio-demographic elements of patients with the disease. Even though breast cancer incidence has increased rapidly in Ethiopia [13], there is still lack of studies that investigated socio-demographic and haematological profile of breast cancer patients. It is important to assess haematological status of breast cancer patients at regular intervals during different stages of treatment to determine their diagnostic and prognostic values, which can help for improved management. Therefore, this study was aimed to assess socio-demographic and hematologic profiles of patients with breast cancer at Tikur Anbessa Specialised Hospital.

Materials and Methods

Study design and period: Hospital-based case control study was done at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia. The study was conducted from May 2018 to June 2019. Cases and controls were matched based on residence within and outside Addis Ababa.

Eligibility criteria

Since breast cancer mainly affects women, only women patients and controls aged 18 years and older were included in the study. Cases were all newly diagnosed breast cancer patients with confirmed histology result, no recognizable mental illnesses, and no history of chronic illness. On the other hand, controls were women accompanying breast cancer patients who had no biological relationship with selected cases, no history of chronic illness, and who were free from breast mass.

Sampling and sample Size determination

Tikur Anbessa Specialized Hospital was selected for the study since it was the only referral centre for cancer treatment during the study period. All eligible and voluntary breast cancer patients that came to TASH during the study period were included as cases and controls based on convenient sampling technique.

The sample population of the cases was female breast cancer patients referred to TASH Oncology department, who fulfilled inclusion criteria and who gave informed consent. For the controls, the sample population was women caregivers accompanying breast cancer patients.

Sample size was calculated using Open Epi by assuming old age (>50 years) as a risk factor for breast cancer, 80% power, 0.05 significance level at 95% CI, and 1:1 ratio of case to control. Percentage of exposed among control group was 11.9%, percentage of exposed among cases 21.6%, (Ibrahim, 2010), and odds ratio of 2.05. Finally, the total sample size was 460 (230 cases and 230 controls).

Data collection, management, and analysis

Prior to data collection, written informed consent was obtained from each study participant. Haematological parameters of breast cancer patients were recorded from their laboratory reports. Eligible controls were selected by breast physical examination. Then, interview was conducted by experienced nurses. Blood sample was collected at the end of each interview and the sample was analysed at TASH Laboratory using Sysmex KX –21N Haematology analyser. Data was analysed by using Statistical Package for Social Science (SPSS) version 20 Software. Then, descriptive analysis was made to assess socio-demographic characteristics of the study participants. Independent sample t-test was used to compare mean $\pm$ standard deviation of different haematological parameters. In addition, Chi square test was conducted to see significant difference of haematological parameters between cases and controls. P- values less than 0.05 were considered statistically significant.

To assess presence of selected haematologic abnormalities, the reference range was taken from WHO and from the output of CBC SYSMEX KX –21N haematology analyser. Regarding anaemia, WHO 2011 haemoglobin (HB) concentration cut-offs for the diagnosis of anaemia and assessment of severity was used. As per this assessment, if HB concentration is $\geq$12gm/dl, there is no anaemia, HB level 10.9 - 11.0gm/dl is associated with mild anaemia, HB 8.0-10.9 gm/dl suggestive of moderate anaemia and severe anaemia is indicated by HB less than 8gm/dl. In addition, anaemia was further characterised as microcytic and macrocytic based on MCV values; and as hypochromic and normochromic anaemia based on MCHC values. Leucocyte and platelet values were also characterised based on the reference range of haematology analyser. When WBC count was less than 3.7 x 10^9/L, it was characterised as leucopoenia, whereas when the value was greater than 10.4 x10^9/L, it was characterised as leucocytosis. Regarding the platelet count, if the platelet count was less than 140 x 10^9/L, it was characterised as thrombocytopenia; whereas, when the value was greater than 385 x 10^9/L, it was characterised as thrombocytosis.

Data quality control and assurance

To minimise errors when using hospital controls, healthy controls were selected after breast physical examination was made. And to facilitate their understanding of the issues, questionnaire was prepared in English and translated to Amharic. For those who did not speak Amharic language, we used care givers and nurses as translators. Data collection tools were pretested, and training was given for data collectors. Daily supervision was made on all questioners collected on each day. All collected blood specimens were analysed on the same day of sample collection. Control samples were analysed before testing actual patient samples.

Ethical considerations

Ethical approval was obtained from Addis Ababa University, College of Health Sciences Institutional Review Board. Written informed consent was obtained

from each respondent. Confidentiality and privacy were maintained throughout the study. During selection of controls, women who had breast mass were consulted by physician and their results were given for free to get early diagnosis and treatment.

Results

Socio-demographic characteristics of the study participants: In this study, 230 cases and 230 controls were included. Majority (i.e., 70.9%) of the cases and 75.7% of the controls were urban dwellers. Mean ages of the study participants were 42.83 ± 12.06 and 39.33 ± 11.14 years ($P < 0.05$) for cases and controls, respectively. More than half (54.3%) of cases and 62.2% of the controls were less than 40 years old (Table 1). Regarding marital status, 76.1% of the cases and 67.4% of the controls were married. However, nearly half (43.5%) of the cases were not able to read and write, while 30% of the controls had attained secondary education. More than two-third (69.6%) of the cases and 43.1% of the controls were housewives. Even though limited number of study participants replied to the question about their income, 34.3% of the cases and 12.6% of the controls had less than 1000 Ethiopian Birr per month (Table 1).

Table1. **Socio demographic characteristics of study participants at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2019**

Variables	**Cases**		**Controls**	
Residence	**Frequency**	**Per cent**	**Frequency**	**Per cent**
Urban	163	70.9	174	75.7
Rural	67	29.1	56	24.3
Age group (years)				
<40	125	54.3	143	62.2
40 and above	105	45.7	87	37.8
Mean age (Mean ±SD)	42.83 ± 12.06		39.33 ± 11.14	
Marital status				
Single	23	10.0	29	12.6
Married	175	76.1	155	67.4
Divorced/widowed	32	13.9	46	20.0
Education level				
Not able to read and write	100	43.5	34	14.8
Able to read and write	26	11.3	9	3.9
Primary education	33	14.3	56	24.3
Secondary education	45	19.6	69	30.0
College and University	26	11.3	62	27.0
Occupation				
Housewife	160	69.6	99	43.1
Government employee	34	14.8	70	30.4
Private	16	7.0	42	18.2
Other	20	8.6	19	8.3
Income (ETB)	**(N=108)**		**(N=127)**	
< 1000	37	34.3	16	12.6
1000 -2000	32	29.6	37	29.1
2001-3000	10	9.3	27	21.3
Greater than 3000	29	26.9	47	37.0

Haematologic profile of breast cancer cases and controls

Haemoglobin, red blood cells, platelet count and packed cell volume: The overall mean values with standard deviation of HB, RBC, PCV, of cases were (13.1 ± 1.6g/dl, 4.6 ± 0.54 x 10^{12}/L and 38.7 ± 4.5 %, respectively and those values for controls were 14.0 ± 1.3g/dl, 4.8 ± 0.47 x 10^{12}/L, 40.5 ± 3.5%, respectively (Table 2). On the other hand, mean platelet count for the cases and controls were 323.4 ± 108.1x10^{9}/L and 282.0 ± 70.0 x 10^{9}/L, respectively.

Table 2. **HB, RBC, platelet count and PCV parameters of cases and controls at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2019**

Parameter	Cases	Controls	P – value
HB (Mean±SD) g/dl	**13.1±1.6**	**14.0± 1.3**	**0.0001**
Minimum HB	8.7	7.3	
Maximum HB	16.4	20.1	
RBC (Mean±SD) x 10^{12}/L	**4.6±0.54**	**4.8±0.47**	**0.020**
Minimum RBC	2.84	3.39	
Maximum RBC	6.18	7.12	
Platelet (Mean±SD) x 10^9L	**323. 4±108.1**	**282.0±70.0**	**0.0001**
Minimum Platelet	110.0	119.0	
Maximum Platelet	827.0	469.0	
PCV (Mean±SD) %	**38.7±4.5**	**40.5±3.5**	**0.0001**
Minimum PCV	26.20	24.80	
Maximum PCV	49.20	58.40	

Red cell induces.

The overall MCV, MCH and MCHC values were 84.3 ± 8.1fl, 29.0±4.2pg, and 33.7 ± 1.7% for the cases and 85.7 ± 6.0 fl, 29.5 ± 2.4pg, 34.2 ± 2.5% for the controls (Table 3). MCV and MCHC values were significantly lower among breast cancer patients (P <0.05) (Table 3).

Table 3. **Red cell indices values of study participants at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2019**

Red cell indices parameters	Cases	Controls	P- value
MCV, fl (Mean±SD)	**84.3±8.1**	**85.7±6.0**	**0.042**
Minimum MCV	65.6	62.4	
Maximum MCV	105.9	111.5	
MCH, pg (Mean±SD)	**29.0±4.2**	**29.5±2.4**	**0.153**
Minimum MCH	21.2	19.3	
Maximum MCH	37.5	39.2	
MCHC, gm/dl (Mean±SD)	**33.7±1.7**	**34.2±2.5**	**0.005**
Minimum MCHC	22.4	29.4	
Maximum MCHC	38.5	36.6	

Key= *MCV* = Mean Cell Volume; *MCH*= Mean Cell Haemoglobin, *MCHC*= Mean Cell Haemoglobin Concentration, SD= *Standard deviation, fl = femtoliter, pg = pico gram*

Total WBC and WBC differential parameters: In this study, the mean value of total WBC was 7.1 ± 2.8 and 7.1 ± 2.4 x 10^9/L for cases and controls, respectively. The mean neutrophil, lymphocyte, monocyte and eosinophil counts (55.19 ± 13.96%, 29.67 ± 11.21%, 10.14 ± 5.54%, and 4.05 ± 4.65%, respectively) of the cases were, significantly higher than the mean counts for the controls, which were 36.39 ± 19.27%, 24.58 ± 8.40%, 5.51 ± 2.08%, and 2.80 ± 3.88%, respectively.

Characterization of some selected hematologic parameters: In this study, 20.4% of the cases and 5.6% of the controls were anaemic based on their haemoglobin value. Based on severity of anaemia, 11.7% of the cases and 1.7% of the controls were moderately anaemic. On the other hand, 8.7% of the cases and 3.5% of the controls were mildly anaemic (P=0.0001) (Table 4).

Table 4. **Distribution of abnormal haemoglobin, leucocyte and platelet values between breast cancer cases and controls at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2019**

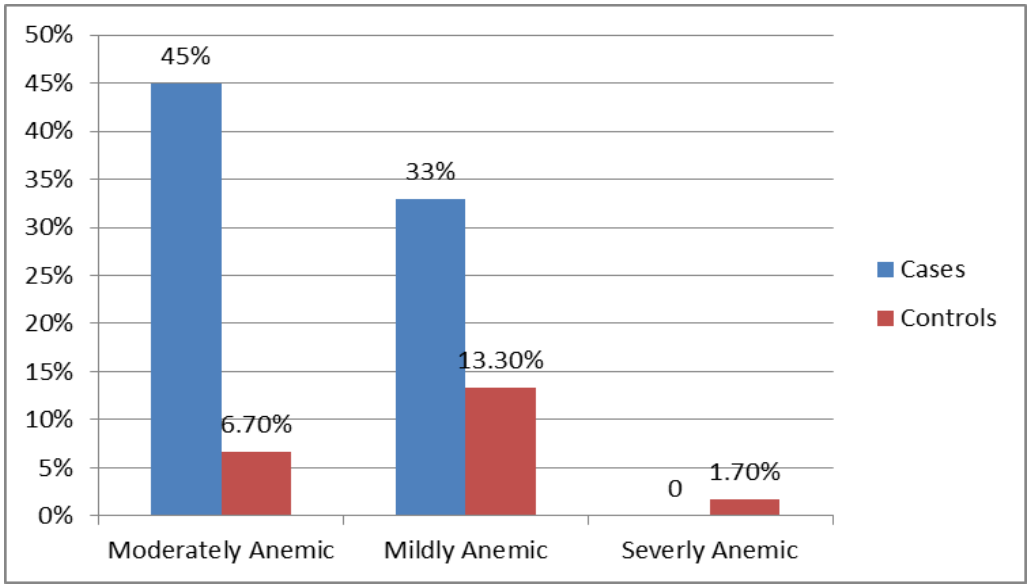
Parameters	**Cases**		**Controls**		**P - value**
Haemoglobin (gm/dl)	***N***	***%***	***N***	***%***	
12 and above (No anaemia)	183	79.6	217	94.3	
Mild anaemia	20	8.7	8	3.5	0.0001
Moderate anaemia	27	11.7	4	1.7	
Severe anaemia	0	0	1	0.4	
Microcytic anaemia	64	28.2	42	18.4	
Macrocytic anaemia	2	0.9	3	1.3	0.046
Hypochromic anaemia	15	6.6	8	3.5	0.134
Normocytic anaemia	23	10.0	7	3.0	0.003
Normochromic anaemia	27	11.7	9	3.9	0.002
Microcytic Hypochromic	9	3.9	4	1.7	0.159
Leucopoenia	13	5.7	9	3.9	0.681
Normal	198	86.1	202	87.8	
Leucocytosis	19	8.3	19	8.3	
Thrombocytopenia	4	1.7	5	2.2	
Normal	172	74.8	207	90	0.0001
Thrombocytosis	54	23.5	18	7.8	
Both anaemic and thrombocytosis	16	7.0	1	0.4	0.0001
Both anaemic, thrombocytosis and leucocytosis	5	2.2	0	0.0	0.025

**The reference range is based on the WHO classification of anaemia. Regarding leucocyte and platelet, the reference range is based on the established range of the CBC Sysmex* KX – 21N *haematology analyser.*

**Anaemia, When HB<12gm/dl, (Mild anaemia when HB is 10.9-11.0 gm/dl, Moderate anaemia when HB is 8.0-10.9 gm/dl, and Severe anaemia when HB is <8 gm/dl)*

** Leucocytosis: when total WBC count is >10.4 x 10^9/L, Leucopoenia: when total WBC count is < 3.7 x 10^9/L.*

Out of the total anaemic study participants, 33.3% of the cases and 13.3% of the controls were mildly anaemic. Moderately anaemic participants accounted for 45% of the cases and 6.7% of the controls. Only 1.7% of the control group were severely anaemic (Figure 1).



***Classification of Anaemia:** *When HB<12gm/dl, (Mild anaemia when HB is 10.9-11.0 gm/dl, Moderate anaemia, when HB is 8.0-10.9 gm/dl, and Severe anaemia when HB is <8 gm/dl)*

Figure 1. **Severity of anaemia among breast cancer cases and controls at Tikur Anbessa Specialized Hospital, Addis Ababa, 2019**

Regarding characterisation of anaemia, microcytic anaemia was found among 28.2% of the cases and 18.4% of the controls. However, microcytic anaemia was found among 0.9% of the cases and 1.3% of the controls. Similarly, 6.6% of the cases and 3.5% of the controls had hypochromic anaemia. It was also found that 10.5% of the cases and 3% of the controls were with normocytic anaemia; 11.7% of the cases and 3.9% of the controls were with normochromic anaemia and 3.9% of the cases and 1.7% of the controls were with microcytic hypochromic anaemia (Table 4). Thrombocytosis was found among 23.5% of the cases and 7.8% of the controls (P=0.0001) (Table 4). The finding also indicated that 7.0% of the cases and 0.4% of the controls were both anaemic and with thrombocytosis (P=0.0001). Similarly, 2.2% of the cases and none of the controls had the triple burden of anaemia, leucocytosis, and thrombocytosis (Table 4).

Discussion

Breast cancer is a major public health problem among women both in developed and developing countries. Its incidence is rapidly increasing [1-3]. In general, different socio demographic and hematologic characterisations are important and should be considered to maximise treatment success and patient survival. In this study, 54.3% of the study participants were less than 40 years of age. This finding is comparable with different studies conducted in Ethiopia [11,12, 25] but not with a study conducted in Iraq [20]. This difference could be due to lifestyle, diet, genetic characteristics, population characteristics and related factors. Even though breast cancer incidence is supposed to be higher in above 50 years of age, in this study, 15.2% of cases were found to be less than 30 years old, which is comparable with another study done in Ethiopia [25]. However, this study is incomparable with a study done in India, which indicated that there is no breast cancer case among those that were under 30 years of age; this difference, could be due to lifestyle, genetic factors, and the population distribution of the country [21]. In general, this study revealed that the majority (that is 76.5%) of breast cancer patients were less than 50 years old. This finding is somehow comparable with a study done in Pakistan [26].

Regarding educational status, 43.5% of the cases and 14.8% of the controls were not able to read and write. This result is not comparable with findings reported in Sindh. The difference could be due to smaller sample size and study setting (26). In general, large proportion (34.3%) of cases as opposed to 12.6% of the controls had a monthly income of less than 2000 Ethiopian Birr. However, another study indicated that the prevalence of breast cancer was higher among socioeconomically better off individuals, presumably due to lifestyle risks they are exposed to [27]**.** The majority (i.e., 76.1%) of the cases were married. That seems to be consistent with results of studies done in Bagdad and Pakistan [6, 26].

Haematological parameters are examinations which are usually accessible with minimum costs. These parameters provide helpful evidence regarding many types of illnesses, including cancer [20]. This study found that the mean HB, PCV, and RBC counts were significantly lower in patients than in controls. This finding is consistent with studies done in Iraq [20], Nigeria [18], and Sindah [26].

Since HB and PCV are used as guides to diagnose anaemia, which is one of the major problems among most of the cancer patients, those parameters were usually lower for the cases than for the healthy controls [18, 26]. This low level of haematological parameters may be associated with bone marrow or immune suppression, because of the cancer itself [18]. The other possible reason could be if the patients were on pre- or post-surgery conditions, these parameters can be significantly reduced. In addition, nutritional status and clinical conditions of patients could also play important role in the reduction of such values [28, 29]. The mean MCV and MCHC were significantly lower among cases than among controls. This finding is in conformity with results of a study done in Nigeria [19]. Except for MCH, it is also supported by a study done in India [30].

The mean platelet count was significantly higher among patients than controls. This finding is comparable with similar studies done in India and Nigeria [16, 19]. This increment could be explained by the reactive thrombocytosis among most breast cancer patients because of cancer-induced anaemia. However, this finding is divergent from results of similar study conducted in Iraq [20]. This difference could be due to small sample size, clinical characteristics, and demographic differences of the study participants. In this study, the mean neutrophil and lymphocyte counts were higher among the cases than with the controls, and the higher counts could be explained by neoplasm of cancer cells. This finding is consistent with a study conducted in Nigeria [19]. In this study, anaemia was found in 20.4% of the cases and 5.6% of the controls, a result which conforms with similar studies conducted in Ethiopia and China [31, 32].

In contrast to the current study, researchers from India reported that 60% of pre-chemotherapy breast cancer patients were anaemic [28]. This inconsistency in the findings could be due to smaller sample size of the Indian study, due to difference in study set up and background of the study participants. This study also indicated that leukopenia was found in 5.7% of the cases and 3.9% of controls. The finding is nearly comparable with a study done in India [33]. Thrombocytosis was observed among 23.5% of the cases and 7.8% of the controls. This study was also nearly comparable with a study done in Switzerland [34].

Limitations

This study is a hospital-based investigation; its results may not hold for the general population. In addition, even though breast physical examination was made by experienced physician, physical examination may not be sufficient to detect potential breast mass.

Conclusion and Recommendations

This study observed that most of the breast cancer patients were young and there were significant numbers of breast cancer cases even under the age of 30 years. More than two-fifths (43%) of breast cancer cases were not able to read and write, with low monthly income. Regarding haematological parameters, the mean haemoglobin, red blood cell count, packed cell volume, mean corpuscular volume; and mean corpuscular haemoglobin concentration values were significantly lower among cases compared to controls. On the other hand, some haematological parameters like platelet count, neutrophil count, are significantly higher among controls. Anaemia and thrombocytosis were also observed as major hematologic abnormalities among breast cancer patients.

Since younger women were highly affected by breast cancer, attention should be given by concerned bodies for the young population in every aspect of prevention and control activities of breast cancer. Since this study may not provide representative evidence, it is important to conduct further studies with large sample size to confirm the findings of this study and design appropriate interventions.

Conflict of Interests

- All authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contribution:

- I state that this research was done by all authors indicated in this article. All of the authors participated starting from conception and design the study through the preparation of this manuscript. Finally, all authors critically reviewed and approved the manuscript.
- This study may help to identify the target group for counselling and awareness creation, depending on their needs in the general population.

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Association of risk factors and breast cancer among women treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: a case–control study

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ABSTRACT

Objectives Many factors known to increase the risk of breast cancer, such as age, family history, early menarche and late menopause are not modifiable. Modifiable factors include obesity, use of menopausal hormones and breast feeding. This study aimed to assess risk factors associated with breast cancer among women at Tikur Anbessa Specialized Hospital.

Design Facility based case–control study.

Methods Case–control study was conducted from May 2018 to June 2019. A total of 230 cases and 230 controls participated in the study. Data were analysed using SPSS software. Multivariable logistic model based analysis was conducted to control the effect of potential confounding factors. ORs and 95% CI for the likelihood of developing breast cancer were calculated.

Results The odds of breast cancer was higher among women between 40 and 49 years (adjusted OR (AOR): 3.29, 95% CI 1.39 to 7.77), and being unemployed (AOR: 4.28, 95% CI 2.00 to 9.16). Regarding life style risk factors, women consuming solid oil and using wood or animal dung as source of fuel had significantly higher odds of breast cancer. In addition, the odds of breast cancer was significantly higher among postmenopausal women, women who had previous benign surgery and women with early menarche (<12 years). On the other hand, the odd of breast cancer was significantly lower among women who had moderate physical activities.

Conclusion This study showed that occupational status, consumption of solid oil, and using wood or animal dung as source of fuel, early menarche, menopausal status and previous benign breast surgery were associated with breast cancer. On the other hand, physical activity was protective factor. Therefore, there is a need to design appropriate intervention to educate women about life style change or behaviour modification to decrease their breast cancer risk.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To our knowledge this was the first research conducted among breast cancer patient in Ethiopia at the time of the study.
⇒ During selection of control group, breast physical examination has been made by experienced oncology resident.
⇒ Further analysis was not conducted by different ethnic group due to limited sample size and shortage of budget.
⇒ Even though breast physical examination may be the only available breast cancer screening modality in resource limited countries like Ethiopia, and it has been made by experienced physician, it may not be highly sensitive to detect potential breast mass.

BACKGROUND

There are several established risk factors for breast cancer. Most factors which increase the risk of breast cancer are not modifiable; these include age, family history, early menarche and late menopause. Factors that are modifiable include postmenopausal obesity, postmenopausal hormonal replacement therapy and breast feeding. Genetic risk factors like mutations in BReast Cancer gen 1 and BReast Cancer gen 2 are also the most prominent cause of breast cancer.[1 2] This is established through studies conducted in various countries.[3]

Similarly study from Tanzania found that women who had their first full-term pregnancy at <30 years were more likely to have luminal-B and triple negative subtypes relative to luminal-A subtype.[4] Another study done in Cairo also revealed that the most common risk factors for breast cancer were family history of breast cancer and using hormonal contraceptives.[5]

Breast cancer poses a substantial public health threat in Ethiopia.[6] According to Addis Ababa City Cancer Registry, breast cancer accounts, 33% of cancers among females.[7] However, based on various studies conducted in the country there was poor community awareness towards the disease.[8 9] Most patients and their families do not properly know about cancer and its treatment options. As a result, 80%–90% of cancer patients

already suffer from advanced and incurable cancers at the time of diagnosis.[9 10]

Even though many studies found different risk factors, such risk factors are not studied well, especially for most resource limited countries. For a country like Ethiopia with a huge population, different, ethnic geographical variations, life style and cultural habits, information on breast cancer associated risk factors are significantly limited. Targeting and supporting these populations to reduce their risk is an essential component of population health. Therefore, this study was aimed to assess risk factors for breast cancer among women at Tikur Anbessa Specilaized Hospital. The result of this study will help to identify possible risk factors which can be used for policy makers to raise community awareness, for reduction in morbidity and mortality.

MATERIALS AND METHODS

Study design and period

Facility based case–control study was conducted between May 2018 and June 2019 in Addis Ababa at Tikur Anbessa Specialized Hospital (TASH) Oncology Department, which is the largest hospital in Ethiopia with 700 beds.[11] This hospital is the country's sole cancer referral centre which provides surgery, chemotherapy, radiotherapy and palliative care.

Eligibility criteria

During the study period, all consenting newly diagnosed breast cancer patients, with confirmed histology result, no observable mental disorders, no history of chronic disease and aged 18 years and above were included in the study. Women accompanying breast cancer patients who had no biological relationship with selected cases were included as a control in the study. Controls were breast mass free women by physical examination.

Sampling and sample size determination

Since there was only one referral centre for cancer treatment during the study period, the existing centre (TASH) was used for the study. All voluntary and eligible cases and controls that came to TASH during the study period were recruited by using convenient sampling technique. Sample size was calculated by taking age (≥65 years) as a risk factor for breast cancer, 80% power, 0.05 significance level at 95% CI and 1:1 ratio of case to control. Percentage of exposed among control group was 11.9%, percentage of exposed among cases was 21.6%[12] and OR of assumed to be 2.05. Accordingly, a total of 460 participants (230 cases and 230 controls) participated in this study.

Data collection analysis and management

Informed consent was obtained from each study participant prior to data collection. Participants were interviewed by experienced and trained nurses in a convenient place to maintain privacy and confidentiality. Breast physical examination was conducted by oncology residents in order to select eligible controls. Data entry and analysis was done using SPSS Software, V.20. Binary logistic regression was conducted to see the association between breast cancer and risk factors. Finally, stepwise multivariable analysis was done to adjust for potential confounding variables by selecting variables which have p value ≤0.05 in bivariate analysis. The association between breast cancer and different variables was assessed. These variables include socio demographic variables including age, educational status, occupational status and income. Anthropometric and life style variables included in the model were, weight, body mass index (BMI), fruit intake, milk intake, consumption of solid/saturated oil, source of fuel, frequency of strenuous exercise and frequency of moderate exercise. In addition, age at menarche, menopausal status, family history with first degree relatives, and previous benign disease/previous breast srgery were also included. P value less than 0.05 were considered as statistically significant while adjusted ORs with 95% CI were used to see the strength and direction of the association.

In our analysis, potential confounding variables associated with breast cancer were included in the stepwise multiple logistic regression model. After this analysis, income, educational status, height, weight, BMI, fruit intake and frequency of strenuous exercise wereconsidered as potential confounding variables.

When conducting logistic regression analysis, for most of the study variables, reference group was selected by considering the most normative group or if the group is considered as preventive factor for negative outcomes. However, for some variables like weight and BMI, the highest category was considered as a reference category, since there was inverse relationship between higher BMI and higher weight in our study. For some variables including consumption of vegetable, fruit, meat and milk, the lowest category was considered as references based on similar studies.

Study variables

Based on American Cancer Society fact and figure for breast cancer, age at diagnosis was categorised as less than 40, 40–49, 50–59 and 60 years and above. BMI was calculated and categorised as follows <25 normal, 25–29.9 overweight and >30 obese. Menarche was defined as the age at which the first menses was occurred. Age at first live birth was defined as the age when the first full-term birth occurred. Abortion was defined as the termination of pregnancy before 28 weeks of pregnancy. Parity was defined as the number of pregnancies that a participant had. Women who had sisters/mothers/daughters with breast cancer were categorised as having a first-degree family history of breast cancer. Women were classified as menopausal if they had not menstruated during the past 1 year before the date of data collection. Breast surgery was defined as weather study participant had surgery for non-cancer lump.

Data quality assurance

The data collection tools were prepared in English and translated to the local language in order to facilitate understanding by the study participants. The data collection tools were pretested in 5% of breast cancer patients not included in the study. Daily supervision was made on all questionnaires collected each day. This research was conducted based on research requirements, regulations and policies that safeguard the well-being of study participants and to ensure the reliability and integrity of this finding. Therefore, all methods were carried out in accordance with relevant guidelines and regulations.

Patient and public involvement

Neither patients nor the public were involved in the design of this study.

RESULTS

Bivariate analysis of sociodemographic characteristics and anthropometric factors

In this study, a total of 230 breast cancer cases and 230 healthy controls were participated. The mean age (±SD) was 42.83±12.06 for cases and 39.33±11.14 years for controls. The odds of breast cancer was significantly higher among women aged 40–49 and >60 years. The odds of developing breast cancer among illiterate was 4.43 times higher (95% CI 2.83 to 6.94, p=0.0001) compared with literate women. Similarly, the odds of breast cancer was also 3.03 times higher (95% CI 2.06 to 4.44, p=0.0001)) among unemployed women as compared with employed. It was also 2.43 times (95% CI 1.43 to 4.14, p=0.001) higher among women with lower conomic status as compared with women with higher economic status (monthly income >2000 Ethiopian Birr) per month. However, there was no significant association between breast cancer with place of residence and marital status. The odds of breast cancer was 2.13 times higher (95% CI. 1.06 to 4.28, p=0.034) among women with less than 59 kg as compared with women greater than 75 kg. Similarly, the odds of breast cancer was 2.48 times higher (95% CI 1.07 to 5.75, p=0.035) among women with BMI 25–29.9 kg/m^2 (table 1).

Table 1 Sociodemographic characteristics and anthropometric risk factors associated with breast cancer

Variables	Case N (%)	Control N (%)	Bivariate analysis COR (95% CI)	P value
Residence				
Rural	67 (29.1)	56 (24.3)	1:00	
Urban	163 (70.9)	174 (75.7)	0.783 (0.517 to 1.19)	0.247
Age group (years)				
<39	106 (46.1)	136 (59.1)	1:00	
40–49	58 (25.2)	45 (19.6)	*1.65 (1.04 to 2.63)*	0.034
50–59	39 (17.0)	36 (15.7)	*1.39 (0.827 to 2.34)*	0.214
>60	27 (11.7)	13 (5.7)	*2.67 (1.31 to 5.41)*	0.007
Marital status				
Ever married	207 (90.0)	201 (87.4)	1:00	
Never married	23 (10.0)	29 (12.6)	0.770 (0.431 to 1.38)	0.378
Education level				
Literate	130 (56.5)	196 (85.2)	1:00	1:00
Illiterate	100 (43.5)	34 (14.8)	4.43 (2.83 to 6.94)	0.0001
Occupation				
Employed	70 (30.4)	131 (57)	1:00	1:00
Unemployed	160 (69.6)	99 (43.0)	3.03 (2.06 to 4.44)	0.0001
Income	(N=108)	(N=127)		
≥2000	52 (48.1)	88 (69.3)	1:00	1:00
<2000	56 (51.9)	39 (30.7)	2.43 (1.43 to 4.14)	0.001
Height (m)				
≥1.60	102 (44.3)	91 (39.6)	1:00	1:00
<1.52	48 (20.9)	32 (13.9)	1.34 (0.788 to 2.27)	0.280
1.53–159	80 (34.8)	107 (46.5)	0.667 (0.445 to 1.00)	0.050
Weight (kg)				
>75	14 (6.1)	25 (10.9)	1:00	
<59	143 (62.2)	120 (52.2)	2.13 (1.06 to 4.28)	0.034
59.1–65	37 (16.1)	52 (22.6)	1.27 (0.583 to 2.77)	0.546
65.1–74	36 (15.7)	33 (14.3)	1.95 (0.869 to 4.36)	0.105
BMI (kg/m^2)				
Obese (>30)	10 (4.3)	22 (9.6)	1:00	
25–29.9 (overweight)	54 (23.5)	48 (20.9)	2.48 (1.07 to 5.75)	0.035
Normal (<25)	166 (72.2)	160 (69.6)	2.28 (1.05 to 4.97)	0.038

Bivariate analysis using binary logistic regression. 1:00 is OR for reference/comparison group.
BMI, body mass index; COR, crude OR.

Life style risk factors associated with breast cancer

In this study, neither cases nor controls had used horone replacemnet therapy (HRT). On the other hand, three cases and none of the controls were smokers. However, 49 (21.3%) of cases and 66 (28.7%) of the controls had a history of alcohol consumption. Regarding dietary habit, there was no significant association between vegetable and meat intake with breast cancer. This study also indicated that the odd of breast cancer was 4.04 times higher among women who had used solid oil. Similarly, the odd of breast cancer was 6.46 times higher among women who had used wood or animal dung as compared with use of electric as a source of fuel. Regarding physical activity, women who had strenuous physical activities like running, swimming less than 5 hours per week had 0.343 times lower risk of breast cancer. Similarly, women who had moderate physical activity such as walking, playing tennis less than 5 hours per week had 0.228 times less risk (table 2).

Reproductive risk factors associated with breast cancer

In this study, the odds of breast cancer was 3.16 times higher among women who had age at menarche less than

Table 2 Association of life style risk factors with breast cancer

Variables	Case N (%)	Controls N (%)	Bivariate analysis	
			COR (95% CI)	P value
Smoking				
No	227 (98.7)	230 (100)	1:00	
Yes	3	0 (0.0)	1.01 (0.998 to 1.03)	0.082
Alcohol intake				
Non-drinker	181 (78.7)	164 (71.3)	1:00	
Drinker	49 (21.3)	66 (28.7)	0.673 (0.439 to 1.03)	0.068
Vegetable intake				
Once a week or less	166 (72.2)	158 (68.7)	1:00	
More than once a week	64 (27.8)	72 (31.3)	0.846 (0.567 to 1.26)	0.414
Fruit intake				
Once a week or less	194 (84.3)	210 (91.3)	1:00	
More than once a week	36 (15.7)	20 (8.7)	1.95 (1.09 to 3.48)	0.024
Meat				
Once a week or less	207 (90.0)	218 (94.8)	1:00	
More than once a week	23 (10.0)	12 (5.2)	2.02 (979 to 1.4.16)	0.057
Milk take				
Once a week or less	189 (82.5)	207 (90.8)	1:00	
More than once a week	40 (15.7)	21 (9.2)	2.086 (1.19 to 3.67)	0.011
Solid oil				
No	45 (19.6)	114 (49.6)	1:00	
Yes	185 (80.4)	116 (50.4)	4.04 (2.67 to 6.12)	0.0001
Source of fuel				
Electric	54 (23.5)	111 (48.3)	1:00	
Wood/animal dung	88 (38.3)	28 (12.2)	6.46 (3.78 to 11.03)	0.0001
Charcoal/kerosene	3 (1.3)	20 (8.7)	0.308 (0.088 to 1.08)	0.066
Combination	85 (37.0)	71 (30.9)	2.46 (1.57 to 3.87)	0.0001
Strenuous exercise				
No exercise	209 (90.9)	203 (88.3)	1:00	
<5 hours per week	6 (2.6)	17 (7.4)	0.343 (0.133 to 0.887)	0.027
5 hours and above per week	15 (6.5)	10 (4.3)	1.46 (0.640 to 3.32)	0.370
Moderate exercise				
No exercise	173 (75.2)	126 (54.8)	1:00	
<5 hours per week	21 (9.1)	67 (29.1)	0.228 (0.133 to 0.392)	0.0001
5 hours and above per week	36 (157)	37 (16.1)	0.709 (0.424 to 1.18)	0.188

Bivariate analysis using binary logistic regression. 1:00 is OR for reference/comparison group.
COR, crude OR.

12 years. On the other hand, there was no significant association between abortion, as well as age at first birth with breast cancer. Similarly, the odds of breast cancer was 2.34 times higher among postmenopausal women. In addition, women who had previous breast surgery were 8.82 times more likely to develop breast cancer. However, there was no statistically significant association between breast cancer and age at menopause, use of oral contraceptive, duration of breast feeding and age at last birth. However the association between breast cancer with family history of first degree relatives was declined after stepwise multiple logistic regression models was applied (table 3).

Multivariable analysis of sociodemographic, anthropometric and lifestyle factors

The finding indicated that the odds of breast cancer were 3.29 times higher among women with 40–49 age groups as compared with women 39 years or less. It was also found that the odds of breast cancer were 4.28 times

Table 3 Association of reproductive risk factors with breast cancer

Parameter	Case N (%)	Control N (%)	Bivariate analysis		Multivariable analysis	
			COR (95% CI)	P value	AOR (95% CI)	P value
Age at menarche (years)						
>15	20 (11.2)	60 (28.6)	1:00		1:00	1:00
12–15	150 (83.8)	144 (68.6)	3.13 (1.79 to 5.45)	0.0001	5.94 (1.84 to 19.15)	0.003
<12	9 (5.0)	6 (2.9)	4.50 (1.42 to 14.21)	*0.010*	*3.16 (1.78 to 5.56)*	*0.001*
Family history of breast						
No	215 (93.5)	226 (98.3)	1:00		1:00	1:00
Yes	15 (6.5)	4 (1.7)	3.94 (1.29 to 12.07)	0.016	2.60 (0.765 to 8.81)	0.126
Menopausal status						
Premenopausal (ref.)	122 (53.0)	161 (70.0)	1:00		1:00	1:00
Postmenopausal	108 (47.0)	69 (30.0)	2.06 (1.41 to 3.03)	0.001	2.34 (1.50 to 3.64)	0.001
History of benign breast disease						
No	211 (91.7)	226 (98.3)	1:00		1:00	1:00
Yes	19 (8.3)	4 (1.7)	5.09 (1.70 to 15.19)	0.004	8.82 (1.96 to 39.60)	0.005

Stepwise multiple logistic regression. 1:00 is OR for reference/comparison group.
Adjusted for: age at menarch, menoposal status, history of surgery and family history with first degree relatives.
AOR, adjusted OR; COR, crude OR.

higher among unemployed women. Regarding life style, milk intake and consumption of solid oil was significantly associated with breast cancer. Similarly, the odd of breast cancer was 5.30 times higher among women who had used wood or animal dung as source of fuel as compared with women who used electric. On the other hand, the odds of breast cancer were 0.276 times lower among women who had moderate physical activities like swimming, table tennis and basketball less than 5 hours per week as compared with women who had no history of exercise. However, the association between breast cancer with educational status, income, height, weight, BMI and frequency of strenuous exercise was declined after stepwise multiple logistic regression models was applied (table 4).

DISCUSSION

In this study, potential risk factors associated with breast cancer were examined. This study revealed that various risk factors, including demographic, life style, reproductive, hormonal factors, are associated with incidence of breast cancer.[13 14]

There was no significant association between place of residence and marital status and risk of breast cancer in our study. This finding was supported by study from Uganda.[15] However, it is different a study done in India that showed significant relationship between breast cancer and being married.[16] The odd of breast cancer was higher among women aged between 40 and 49 years. Similarly, the odd of breast cancer was 4.43 times higher among illiterate compared with literate women. This finding is supported by a similar study done in Bangui, which indicated that the odd of breast cancer was higher among illiterate.[17] However, this association was declined after stepwise multiple logistic regression model was applied. It was also found that the odd of breast cancer was 4.28 times higher among unemployed compared with employed women. This might be due to employed women may have more family income and they may spend money for screening and medical care. Early screening (early screening identify cancer at early stage) as a result of their better economic level and awareness could explain such difference. This finding is also supported by the previous study done in Bangui.[17] However, the current study was incomparable with another study in India which reported a higher risk of breast cancer among women with higher educational status.[18]

Even though, BMI was associated with increased risk of breast cancer,[19] in this study, both weight and BMI of cases were lower than controls. This lower weight and BMI among cases could be due to loss of weight among cases as a result of advanced stage of their disease at time of diagnosis. This finding is comparable with the study done in Malaysia.[20] However, there is also a study which had found postmenopausal women with normal BMI and relatively high body fat levels were associated with an elevated risk of invasive breast cancer and the study explained that normal BMI categorisation may be an inadequate proxy for the risk of breast cancer in postmenopausal women.[19] In this study, there was no significant association between alcohol consumption, vegetable and meat intake with breast cancer. However, this finding is not supported by similar studies conducted in different parts of USA, which observed that a higher intake of fruits and vegetables was associated with a lower breast cancer risk.[21–23] This difference could be due to the difference in

Table 4 Association of sociodemographic, anthropometric and lifestyle factors with breast cancer

Variables	Case N (%)	Control N (%)	Bivariate analysis		Multivariable analysis	
			COR (95% CI)	P value	AOR (95% CI)	P value
Age group (years)						
≤39	106 (46.1)	136 (59.1)	1:00		1:00	1:00
40–49	58 (25.2)	45 (19.6)	*1.65 (1.04 to 2.63)*	0.034	*3.29 (1.39 to 7.77)*	*0.007*
50–59	39 (17.0)	36 (15.7)	*1.39 (0.827 to 2.34)*	0.214	*1.81 (0.661 to 4.96)*	*0.248*
>60	27 (11.7)	13 (5.7)	*2.67 (1.31 to 5.41)*	0.007	*2.44 (0.515 to 11.55)*	*0.261*
Occupation						
Employed	70 (30.4)	131 (57)	1:00	1:00	1:00	1:00
Unemployed	160 (69.6)	99 (43.0)	3.03 (2.06 to 4.44)	0.0001	4.28 (2.00 to 9.16)	0.0001
Milk intake						
Once a week or less	189 (82.5)	207 (90.8)	1:00		1:00	1:00
More than once a week	40 (15.7)	21 (9.2)	2.086 (1.19 to 3.67)	0.011	2.56 (1.02 to 6.43)	0.045
Solid oil						
No	45 (19.6)	114 (49.6)	1:00		1:00	1:00
Yes	185 (80.4)	116 (50.4)	4.04 (2.67 to 6.12)	0.0001	6.77 (3.17 to 14.48)	0.0001
Source of fuel						
Electric	54 (23.5)	111 (48.3)	1:00		1:00	1:00
Wood/animal dung	88 (38.3)	28 (12.2)	6.46 (3.78 to 11.03)	0.0001	5.30 (1.59 to 17.64)	0.007
Charcoal/kerosene	3 (1.3)	20 (8.7)	0.308 (0.088 to 1.08)	0.066	0.112 (0.012 to 1.01)	0.051
Combination	85 (37.0)	71 (30.9)	2.46 (1.57 to 3.87)	0.0001	2.45 (1.16 to 5.15)	0.019
Moderate exercise						
No exercise	173 (75.2)	126 (54.8)	1:00		1:00	1:00
<5 hours per week	21 (9.1)	67 (29.1)	0.228 (0.133 to 0.392)	0.0001	0.276 (0.114 to 0.628)	0.002
5 hours and above per week	36 (157)	37 (16.1)	0.709 (0.424 to 1.18)	0.188	0.496 (0.182 to 1.36)	0.172

Stepwise multiple logistic regression. Adjusted for age, income, education, occupation, height, weight, body mass index, fruit intake, milk intake, solid oil intake, sources of fuel, frequency of moderate exercise, frequency of strenuous exercise, 1:00 is OR for reference/comparison group.
AOR, adjusted OR; COR, crude OR.

type, frequency and amount of such fruit and plant based dietary pattern. The other possible explanation could be consumption of such kinds of diet may be limited among study participants due to limited purchasing power.

However, the odd of breast cancer was 2.56 times higher among women who had consumed milk for more than once a week, compared with women who had consumed milk once a week or less. This finding is supported by study done in Western Mexico.[24] Similarly, the Mexico study also support our finding regarding consumption of meat which was not associated with breast cancer.[24] This association with milk intake has been explained that high milk intake results in the consumption of cow oestrogen metabolites as well as a high caloric intake, both of which increasing the risk of breast cancer.[24] However, this finding is not comparable with different studies which revealed that dairy consumption was inversely associated with the risk of developing breast cancer.[25–27] This difference could be due to the amount, dairy-type and time of consuming such products. In this study, there are two unexpected results which had significant association with breast cancer. The first result wasthe odd of breast cancer was 6.77 times higher among women who used solid oil; since it is saturated fat, it may contain other factors which can increase the risk of breast cancer and the finding was supported by study done in China.[28] This finding also supported by study done in USA that revealed consumption of saturated fat is associated with increased breast cancer risk.[29] The second result was that the odds of breast cancer was 5.3 times higher among women who had used wood or animal dung as a source of fuel. This was supported by study done in USA which revealed that indoor burning either wood or natural gas for long time was associated with higher risk of breast cancer.[30]

Based on the result of bivariate analysis, the odds of breast cancer were lower among women who had average duration of strenuous exercise of less than 5 hours per week; however, the association was not significant after adjusted for confounding variables. On the other hand, women who had moderate physical activity of less than 5 hours per week had reduced risk of breast cancer. This finding is comparable with the studies done in UK and

Sudan which indicated that physical activity was associated with a reduction in breast cancer risk.[31 32] And this study also supported by systematic review and meta-analysis conducted in China stated that physical activity is significantly associated with a decrease in the risk of breast cancer.[33]

In this study, only 5.0% of cases and 2.9% of controls had menarche at less than 12 years of age. Late menarche (>15 years) was found to be significant protective factor for breast cancer, compared with earlier age at menarche (<12 years), this finding was supported by study done in Morocco.[34] This finding was also in agreement with study done in UK which found that breast cancer risk increased by a factor of 1.050 (95% CI 1.044 to 1.057; p<0.0001) for every year younger at menarche, and independently by a smaller amount (1.029, 95% CI 1.025 to 1.032; p<0.0001), for every year older at menopause.[35] Our study did not find association with age at first full-term pregnancy, which was different from a study done in Morocco.[34] On the other hand, this finding was comparable with study done in Uganda which revealed absence of association between breast cancer and early age at first pregnancy.[15]

In this study, the odd of breast cancer was 2.34 times higher among postmenopausal women. This finding is comparable with a study done in Malaysia, which indicated that postmenopausal women had 52% increased risk of breast cancer.[20] This finding was also comparable with different studies conducted in India.[3 16] It was also found that 19 (8.3%) of cases and 4 (1.7%) of the controls had previous breast surgery. Women with previous benign breast surgery were 8.82 times more likely to have breast cancer. This finding was supported by studies conducted in India Malaysia and Sudan.[17 20 32]

In our study, oral contraceptive was not significantly associated with breast cancer, which was also supported by other study done in India.[36] However, this finding is not supported by study done in Cameroon[37] and it also contradicts with study in Denmark that found approximately 20% higher risk of breast cancer among women who currently use hormonal contraceptives. Similar studies conducted in India and UK also reported an increased risk of being diagnosed with breast cancer in women who have used hormonal contraception.[16 38 39] This difference could be due to length of contraceptive use and type of contraception. There was no significant association between breast cancer and parity as well as duration of breast feeding, which is comparable with two studies done in India.[14 36]

Study limitation

Some limitations should be considered to elucidate the findings of this study. Primarily the finding of our study was based on self-reporting and that could have introduced recall biases regarding their past exposure for different possible risk factors. This may result under-reporting of the outcome under study. Since this is a case–control study, all the association may not be necessarily casual. The other most important limitation could be even though breast physical examination may be the only available breast cancer screening modality in resource limited countries like Ethiopia, and it has been made by experienced physician, it may not be highly sensitive and may miss a potential breast mass.

Conclusion and recommendation

This study was a case–control study which serves as an indicative study usually used to provide early clues and inform further research using more rigorous scientific methods. In this study, socio demographic, lifestyle, anthropometric and reproductive risk factors were assessed. The finding indicated that the odds of breast cancer decreased among young age and employed women. Regarding lifestyle factors, the odds of breast cancer was 6.8 times higher among women who consumed solid oil. In addition, women who used wood or animal dung as a source of fuel had 5.3 times higher odds of breast cancer. However, the odds of breast cancer decreased among women who had moderate physical exercise less than 5 hours per week. Finally, the odd of breast cancer was higher among women with early menarche (<12 years), postmenopausal women and women with previous benign breast surgery. Since there was significant association between most of the modifiable risk factors and breast cancer, it is essential to design appropriate life style modification strategies which may contribute to prevent breast cancer. There is a need to design appropriate intervention to educate women about lifestyle change or behaviour modification to decrease their breast cancer risk. In addition, since there are varieties of culture, food choice, feeding habit, physical activities and other risk factors, it is important to conduct future studies with a larger sample size including different regions or diverse population in order to come up with more representative evidence.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the School of Public Health Research Ethical Review and the Institutional Review Board of the College of Health Sciences of Addis Ababa University with protocol number 073/17/SPH. Participants gave informed consent to participate before taking part in the study. Written consent was obtained from each of the respondents after the purpose of the study was explained. During breast physical examination for screening of controls, participants who had breast mass were consulted by

physicians and their results were given for free in order to get early diagnosis and treatment. Confidentiality and privacy were maintained throughout the study.

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Data availability statement Data are available upon reasonable request. The data sets used in the current study will be available from the corresponding author on reasonable request.

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RESEARCH ARTICLE

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Adherence to Chemotherapy among Women with Breast Cancer Treated at Tikur Anbessa Specialized and Teaching Hospital, Addis Ababa, Ethiopia

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Abstract

Background: Adherence is important for women with breast cancer because it is a primary determinant for effectiveness of treatment and optimum clinical benefit. Though Breast cancer is the leading cancer in Ethiopia,adherance to chemotherapy is not investigated in Ethiopian women. **Objective:** This study aimed to assess adherence to chemotherapy among women with breast cancer treated at Tikur Anbessa specialized and Teaching Hospital. **Methods:** Cross-sectional study was conducted among 164 breast cancer patients with chemotherapy. After eligible participants were identified, data were collected using face-to-face interviews, card reviews and telephone interviews. Adherence was calculated as the number of doses taken divided by number of recommended or expected doses. Pearson chi-square test was used to evaluate predictors of adherence. **Results:** Among a total of 164 breast cancer patients, majority, 119, (72.6%) of them were urban residents. The mean age of study participants was 41.99 + 10.9 years. The majority 149, (90.9%) of patients were married. More than half 94, (57.3%) of the women were literate. In this study, 137 out of 164 (83.5%) women were adherent to their chemotherapy. Of the 27 non adherent participants. he reason for non-adherence to chemotherapy was unknown for 7, (25.9%) of women. Among different identified reasons for non-adherent, sever illness prevents patients to receive chemotherapy. Based on Pearson chi square test, distance from referral center and treatment regimen were significantly associated with non-adherence rate. **Conclusion:** The present study the results showed that the majority 137, (83.5%) of patients were in good adherence to their chemotherapy. The most identified factor of non-adherence was inability to come for their therapy as a result of severity of illness. Therefore, expansion of cancer diagnosis and treatment centers should be encouraged in order to maximize patient's access and adherence to chemotherapy.

Keywords: Breast cancer- adherence- Non adherence

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Introduction

Breast cancer is the most commonly diagnosed cancer in women. Globally, 24.2%, of all new cancer cases identified in women is breast cancer. It is also the leading cause of cancer death in women, which accounts for15.0% of cancer deaths (WHO, 2018). Adherence can be defined as the extent to which patients follow the instructions they are given for prescribed treatments. This definition was somewhat extended by the WHO as 'the extent to which a person's behavior taking medication, following a diet and/or executing lifestyle changes corresponds with agreed recommendations from a health care provider' (Sabaté, 2003). A Retrospective cohort study of 5,861 women with breast cancer at the Brazilian National Cancer Institute from 2004 to 2010 was conducted to identify factors associated with adherence to hormone therapy. The result revealed that the proportion of adherent patients was 76.3%. There was lower likelihood of adherence among younger women (<40 years), women who were alcohol drinkers, or smokers, and among those who were diagnosed at a non-curable stage. There was also a higher likelihood of adherence among women who had completed second grade or higher education, and among women with a family history of cancer (Claudia et al., 2014).

A population based retrospective observational study conducted in Italy to see the adherence to long-term pharmacological treatment for breast cancer showed that over 46% of patients demonstrated poor/moderate

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adherence, 20% good and only 34% showed an excellent adherence. During the 5 years of follow-up only one woman in every two carried out the adjuvant treatment (Marianna et al., 2013). According to study conducted in South Karnataka, India showed that, even though the treatment options were expensive, family income was not identified as a significant predictor of adherence to treatment. A logistic regression analysis with adherence and different demographic, treatment and disease variables found that spouses support and distant /organ metastasis at the time of diagnosis were significant predictors of adherence to treatment (Nagappa et al., 2012).

Astudy done on adherence to Intravenous Chemotherapy in African-American and Caucasian Women with Early Stage breast cancer found that, 84, (90%) of the sample was adherent to their chemotherapy regimen and only 9(10%) of the sample discontinued chemotherapy prior to completion. For the 44 Caucasian participants, 42, (87.5%) were adherent and 2, (4.3%) were non-adherent. For the 49

African-America participants, 42, (82.4%) were adherent and 7, (13.7%) were non-adherent. No racial difference was found in adherence to chemotherapy between African-American and Caucasian women. Between these two groups, those who were <100% adherent to chemotherapy regimens reported lower income ($p < .001$) (Wells et al., 2015).

Similar study conducted at a breast cancer clinic in Nigeria during a 5-year period (2004-2008) also showed that of the 275 study patients, 79 (28.7%) refused a biopsy sample needed for a definitive diagnosis. Of those who agreed to provide a biopsy sample, 28 patients (10.2%) did not return for a follow-up visit. Mastectomy was offered to 140 patients, 67 of them (47.9%) refused surgery. Of the 53 patients diagnosed with locally advanced lesions offered neo-adjuvant chemotherapy, 15 patients (28.3%) completed the recommended therapy. Of the 44 patients offered adjuvant chemotherapy, 38.6% (17 patients) completed the recommended therapy (Stanley et al., 2011). Among many factors for adherence lack of, getting social support, and thorough therapeutic communication were strongly linked with adherence to them (Wakoet al., 2021). Astudy done in Aira Hospital, rural Ethiopia to assess the feasibility of and adherence to tamoxifen therapy found that among a total of 101 breast cancer patients, 66 (65%) patients were HR+ and were eligible for tamoxifen treatment. However, 15 of the HR+ patients died before tamoxifen became available. Of the remaining 51 HR+ patients, 26 (51%) initiated tamoxifen but only 9 of them (35%) adhered to therapy (medication possession rate ≥80%, median observation 16.2 months). After 1 year, 52% of the patients were still adherent, and 9 patients had discontinued therapy. The reasons for non-initiation of tamoxifen included patient factors, including financial hardship or lack of transportation, and health care provider factors (Reibold et al., 2021).

Even though the trend of breast cancer is increasing in Ethiopia, there is scarcity of data on the adherence of breast cancer patients in order to provide evidence based intervention. Therefore, the aim of this study was to assess the level of adherence to chemotherapy and associated factors among breast cancer patients at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

Materials and Methods

Study setting

This study was conducted in Addis Ababa at Tikur Anbessa Specialized Hospital (TASH) oncology departments. The oncology center which is located and part of TASH and it is the only institution that provides radiotherapy service in Ethiopia. With the support of Ethiopia's governmental institutions, Non-Governmental Organizations (NGOs) and international partners, the hospital is hoping to develop a comprehensive program, including cancer registry, early detection, prevention, standard treatment and palliative care. The hospital has one CT scanner and one MRI scanner. The hospital has 700 beds, of which 18 are allocated for cancer treatment. Of the 201 physicians in the hospital only 2 are hematologists, 4 are medical oncologists, 4 are radiotherapists, 2 are surgical oncologists and one is a pediatric oncologist. Three palliative pain specialists also work at the hospital. Only 26 of the TASH's 627 nurses are dedicated oncology nurses (INCTR, 2015). Tikur Anbessa Specialized Hospital (TASH) was selected for the study, as it it was the only referral center for cancer treatment during the time of data collection.

Study design and population

Hospital based cross-sectional study design was conducted from September 2018 to June 2019. Even though we identified a total of 230 patients, 24, (10.4%) patients were excluded due to incomplete information. In addition, 7(3.0%) patients were considered to be ineligible because of moved to other regional chemotherapy centers and private health facilities and 17, (7.3%) patients were planned for chemotherapy, but they did not start their treatment. Similarly 16, (6.9%) of patients were ineligible because patients were die before initiation of chemotherapy and during the follow-up period. Therefore, the final sample consisted of 164 participants who had complete information.

Data collection, analysis and management

Participants were identified, based on the required criteria, and data were collected by trained oncology nurses during the 3rd, 5th and 7th cycle depending on the type of treatment regimen. In addition card review and telephone interview were applied in order to get complete data. Breast cancer chemotherapy adherence was calculated as the number of doses taken divided by the number of recommended or expected dose. A patient was considered to be non- adherent if she did not present for two consecutive doses of chemotherapy. Patients who had dose reduction and/ or omission due to inadequate hematological profile or poor clinical condition, unplanned public holidays were not included as non-adherent. The patients or patients' family members were contacted via phone calls to supplement the collected data. Some patients were excluded since some patients were moved to private and public health facilities which provide chemotherapy

services in different regions of the country. In addition, some patients, medical records had either incomplete or information totally unavailable, thus Finally, for some patients and their condition was unknown. Finally a total of 164 women with breast cancer were included in this analysis. Bivariate analysis was conducted in order to see the association between different independent variables with adherence. Regarding factors associated with adherence analysis was made based on baseline characteristics. Clinical stage at diagnosis was assigned to each patient based on American Joint Committee on Cancer (TNM) classification scheme , which had indicated that Size and extent of tumor (T), node (N), and metastasis (M).

Ethical consideration and quality assurance

Ethical approval was obtained from Addis Ababa University, College of Health Sciences Institutional Review Board with protocol number 073/17/SPH. Permission was obtained from the Oncology department of TASH. Written informed consent was obtained from each respondent. Confidentiality and privacy were maintained throughout the study. Each interview was transcribed precisely and anonymized to ensure confidentiality by removing any details that might identify any patient or their family. This study was conducted based on research requirements, regulations and policies that safeguard the wellbeing of study participants and to ensure the reliability and integrity of this finding. Therefore, all methods were carried out in accordance with relevant guidelines and regulations.

Results

Socio demographic Characteristics of study participants

In this study a total of 164 breast cancer patients were included of which, total of 119, (72.6%) of the patients were urban residents. The mean age of study participants was 41.99 + 10.9 years. Nearly half, 79, (48.2 %) of women were less than 40 years of age. The majority 149, (90.9%) of patients were married. More than half 94, (57.3%) of the women were literate. The study also showed, majority 119, (72.6%) of women were unemployed. Regarding income, more than half 39 (52.0%) of women earn monthly income of less than 2000 Ethiopian Birr. The result also showed that, more than half, 91, (55.5%) of women were premenopausal. For the majority, 81, (49.3%) of women distance from the referral cancer center is greater than 100 kilometer.

According to the result of Pearson Chi square test, there was no significant difference in the level of adherence based on place of residence and age group of study participants. However, all, 15 (100%) of never married women were adherent to their chemotherapy. In this case the chi-square test showed nearly significant association, (P =0.071). There was also no significant difference in adherence with educational status, employment status, income and menopausal status of women. However, there was significant association between adherence to chemotherapy and distance from the referral cancer center (P = 0.015). Patients who come from a long distance had a significantly lower level of adherence (Table 1).

Distribution of personal characteristics of study participants

In this study 11, (6.7%) of patients had a family history of breast cancer. Even though there was no significant association, patients with a family history of breast cancer were more adherent as compared to those women with no family history of breast cancer. Regarding smoking, only, 3 (1.8%) of breast cancer patients had a history of smoking cigarettes. However, 28, (17.1%) of women had a history of drinking alcohol. Regarding exercise in this study almost one fourth, 39, (23.8 %) of the study participants had experience of moderate exercise. On the other hand only, 12 (7.3%) of women had experience of strenuous exercise before they had been diagnosed with breast cancer. Among a total of 39 women who had experience of moderate exercise, majority, 35 (89.7%) of women adhere to their treatment as compared with only 4 (10.3) women who did not adhere to their treatment. In general there was no statistically significant difference between adherence to chemotherapy with family history, cigarette smoking, alcohol consumption and physical activity (Table 2).

Clinical characteristics of study participants

In this study, 12, (7.3%) of women underwent previous breast surgery, and the adherence level was almost the same between women who underwent previous breast surgery and who had not underwent surgery. The finding also showed that the majority, 73, (44.5%) of women had stage III tumor at diagnosis. Similarly, the commonest pathological diagnosis among the patients was invasive ductal carcinoma, 144, (87.8%). In general there was no statistically significant difference between level of adherence with different stages of tumors and pathological diagnosis. This study also found that, more than half, 104 (63.44%) of patients were planned for eight course of chemotherapy, while 52, (31.7%) and 8, (4.9%) of patients were planned for six and four course regimens of chemotherapy respectively. Based on the Pearson chi-square test, there was a significant difference between the level of adherence and recommended chemotherapy regimen. (Table 3).

Factors associated with non-adherence to chemotherapy

In this study the reason for non-adherence to chemotherapy was unknown for 7, (25.9%) of women. Among different identified reasons for non-adherent cases. Severity of disease /pain was most frequent encountered for 9. (33.3%) of the patients to receive chemotherapy. In addition financial constraints 4, (14.8%), security or distance from cancer referral center, 3, (11.1%) were also identified as factors for non adherence (Table 4).

Discussion

In this study a total of 164 breast cancer women were participated. Based on residence, majority, 72.6 % of women were from urban, which was not comparable with a study done in rural Ethiopia, were only (21%) from urban area, (Reiboldet al., 2021). This difference between studies

Table 1. Socio-demographic Profile of Breast Patients Attending Chemotherapy at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, 2020 (n=164)

Variable	Adherent	None adherent	Total (%)	X^2	P- Vlue
Residence	Frequency (%)	Frequency (%)			
Urban	102 (85.7)	17 (14.3)	119 (72.6)		
Rural	35 (77.8)	10 (22.2)	45 (27.4)	1.49	0.221
Age group (years)					
Less than 40	65 (82.3)	14 (17.7)	79 (48.2)	1.98	0.576
40-49	37 (82.2)	8 (17.8)	45 (27.4)		
50-59	17 (81.0)	4 (19.0)	21 (12.8)		
60 and above	18 (94.7)	1 (5.3)	19 (11.6)		
Marital status					
Ever married	122 (81.9)	27 (18.1)	149 (90.9)	3.25	0.071
Never married	15 (100)	0 (0.0)	15 (9.1)		
Education level					
Illiterate	59 (84.3)	11 (15.7.)	70 (42.7)	0.05	0.823
Litrate	78 (83.0)	16 (17.0)	94 (57.3)		
Occupation					
Employed	37 (82.2)	8 (17.8)	45 (27.4)	0.078	0.78
Unemployed	100 (84.0)	19 (16.0)	119 (72.6)		
Income (n=75)					
<2000	32 (82.1.)	7 (17.9)	39 (52.0)	0.23	0.632
> 2000	31 (86.1)	5 (13.9)	36 (48.0)		
Menopausal status					
Premenopausal	74 (81.3)	17 (18.7)	91 (55.5)	0.731	0.392
Post menopauses	63 (86.3)	10 (13.7)	73 (44.5)		
Distance from referral cancer center					
Near the cancer center	63 (92.6)	5 (7.4)	68 (41.5)	10.46	0.015
< 100 KM	14 (93.3)	1 (6.7)	15 (9.1)		
100-500 Km	44 (74.6)	15 (25.4)	59 (36.0)		
> 500 KM	16 (72.7)	6 (27.3)	22 (13.4)		

X^2, Chi square; %, Percent

Table 2. Personal Characteristics and Level of Adherance among Breast Patients Attending Chemotherapy at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, 2020 (n=164)

Variable	Adherent	None adherent	Total	X^2	P- Value
	Frequency (%)	Frequency (%)			
Family history of breast cancer					
No	127 (83.0)	26 (17.0)	153 (93.3)	0.466	0.495
Yes	10 (90.9)	1 (9.1)	11 (6.7)		
Smoking Cigarettes					
No	134 (83.2)	27 (16.8)	161 (98.2)	0.602	0.438
Yes	3 (100)	0 (0.0)	3 (1.8)		
Alcohol intake					
No	113 (83.1)	23 (16.9)	136 (82.9)	0.116	0.733
Yes	24 (85.7)	4 (14.3)	28 (17.1)		
Moderate exercise					
No	102 (81.6)	23 (18.4)	125 (76.2)	1.43	0.231
Yes	35 (89.7)	4 (10.3)	39 (23.8)		
Strenuous exercise					
No	126 (82.9)	26 (17.1)	152 (92.7)	0.622	0.43
Yes	11 (91.7)	1 (8.3)	12 (7.3)		

X^2, Chi square; %, Percent

Table 3. Clinical Characteristics and Level of Adherence among Breast Cancer Patients Attending Chemotherapy at Tikur Anbessa Specialized Hospital, Addis Ababa Ethiopia, 2020

Variable	Adherent Frequency (%)	None Adherent Frequency (%)	Adherent Total Frequency (%)	X^2	P- Value
Patient with previous breast surgery					
No	127 (83.6)	25 (16.4)	152 (92.7)	0	0.984
Yes	10 (83.3)	2 (16.7)	12 (7.3)		
Stage at diagnosis					
I&II	35 (79.5)	9 (20.5)	44 (26.8)		0.926
III	63 (86.3)	10 (13.7)	73 (44.5)		
IV	39 (83.3)	8 (17.0)	47 (28.7)		
Histology type					
Ductal	121 (84.0)	23 (16.0)	144 (87.8)	0.796	`0.850
Lobular	6 (85.7)	1 (14.3)_	7 (4.3)		
Mixed	5 (83.3)	1 (16.7)	6 (3.7)		
Other/unspecified	5 (71.4)	2 (28.6)	7 (4.3)		
Course of recommended therapy					
Eight	93 (89.4)	11 (10.6)	104 (63.4)	8.5	0.014
Six	37 (71.2)	15 (28.8)	52 (31.7)		
Four	7 (87.5)	1 (12.5)	8 (4.9)		

X^2, Chi square; %, Percent

might be due to the focus of that study being on the rural part of Ethiopia. The mean age of study participants was 41.99 + 10.9 years which was lower than a study done in Northwest Iran where the mean age of study participants was 50.4 years (Dolatkhah et al., 2020). This could be due to the large proportion of women being found at a young age as described in previous studies done in Ethiopia (Tadele, 2015, Abate et al., 2016, Kantelhardtet al., 2014). Nearly half (48.2%) of women were less than 40 years of age, which was also comparable with previous studies done in Ethiopia (Tadele, 2015, Abate et al., 2016, Kantelhardt et al., 2014). It was found that 90.9 % of women were married, which was comparable with study done in rural Ethiopia, (93%) (Reibold et al., 2021), Nigeria (70%) (Ali-Gombe et al., 2021).

In this study, 137 out of 164 (83.5%) of women were adherent to their chemotherapy and 27 (16.5%) women's discontinued their chemotherapy before completion because of different reasons. This finding was lower than a study done on adherence to intravenous Chemotherapy in African-American and Caucasian Women, which was revealed that 90% of breast cancer women were adherent to their chemotherapy (Wells et al., 2015). This difference could be due to that in African-American and Caucasian women study was done among early stage breast cancer patients which might increase patients willingness due to higher probability of good outcome for early stage cancer. The other possible reason could be the study participants might have better chance to get treatment access within a short time due to better infrastructure and adequate health facilities. However this study finding was comparable with the same study done on Caucasian participants, which was 87.5% and 82.4% for African America participants (Wells et al., 2015). On the other hand, this finding was lower than another study done in USA, which had revealed that (88.1 %) completed the prescribed therapy, this difference could be due to the better infrastructure of the study setup and the study was focused on early discontinuation of chemotherapy in women with breast cancer (Neugut et al., 2016). However, this study was comparable with a

Table 4. Factors Associated with Non-adherence to Chemotherapy among Breast Cancer Patients Attending Chemotherapy at Tikur Anbessa Specialized Hospital, Addis Ababa

Variable	Frequency	Percent
Unknown/No response	7	25.9
Severity of disease /pain	9	33.3
Financial constraint	4	14.8
Security issue or distance	3	11.1
Did not believe in chemo/ visit holly water	1	3.7
Pregnancy	1	3.7
Comorbidity	1	3.7
Feels well	1	3.7
Total	27	100

study done in USA, which was found that among a total of 7,399 patients, 1,222 (16.5%) were non adherent cases (Barcenas et al., 2012).

In this study level of adherence was higher among never married women. It was also found that 52.0 % of women earn less than 2000 Ethiopian Birr per month. However, there was no significannt difference in the level of adherence based on monthly income. Regarding menopausal status 55% of women were premenopausal status, which was comparable to study done in rural Ethiopia (47%) (Reibold et al., 2021). The level of adherence was higher among post-menopausal women. This study also found that level of adherence was significantly lower among women who come from long distances from the referral cancer center. This could be due to lack of transport and accommodations. Regarding personal factors, level of adherence was higher among women who had family history of breast cancer as compared to women who did not have a family history of breast cancer. This might be due to women who had family history of breast cancer might have adequate information about the severity of the disease and the importance of treatment. It was also found that there was no statistically significant difference in the level of adherence among women who had a history of smoking as well as drinking alcohol. However level of adherence was higher among women who had experience of moderate as well as extraneous physical exercise.

Regarding clinical characteristics of the current study participants, the majority of women (44.5%) were found to be stage III tumor at diagnosis. Besides, ductal carcinoma was the commonest histology finding. This study finding was comparable with a previous study done in Ethiopia (Kantelhardt et al., 2014). However there was no difference in the level of adherence across tumor grade and tumor pathology/histology. In this study, the majority, 104, (63.4%) of patients recommended eight course chemotherapy, which was not comparable with study done in Nigeria (21.0%). This difference might be due to the different clinical condition of patients. In this study factors related to non-adherence to chemo therapy were assed. However the reason for non-adherence was unknown for a significant number 25.9% of patients. This is because it was difficult to access the patients through their phones in order to know their reason for non-adherence and their current status. Among a total of 27 non adherent women, the majority, 9 (33.3) of women did not adhere their treatment regimen due to the severity of their illness. On the other hand, 3 out of 27 (11.1%) of women did not adhere their treatment. This finding was not comparable with study done in Nigeria, which revealed that financial constraints were the main reasons for non-adherence to chemotherapy for 61% of the patients (Ingwu et al., 2019). This difference could be due to the focus of the Nigeria study was among 100 non adherent women which might explore the potential reasons for non-adherence. Even though their number is limited there were women who did not attend their chemotherapy as a result of financial constraints. Because there was a significant number of patient's living in rural areas, the long distance might prevent them from obtaining health service. Their information about towards breast cancer could also be limited as compared to urban patients.

As a limitation of this study, since it was difficult to get non adherent women, we could not explore different personal and health service related factors which can affect the adherence level of breast cancer patients. There would be potential bias in the data collected using telephone interview and imprecise answers about adherence by relatives of deceased patients. In addition Factors associated with non-adherence were analyzed based on the baseline data which is mainly focused on patient related factors.

In conclusion, the results showed that the majority 137, (83.5%) of patients were in good adherence with their chemotherapy. The most identified factors were inability to come for their therapy as a result of the severity of illness and the residences of patients were long distance from the cancer referral center. For non adherence, distance from referral center and course/regimen of chemotherapy were significantly associated with non-adherence. Therefore, Health care providers should provide adequate information for their patients and establish certain mechanisms for those patients who had withdrawn from their treatment in order to identify reasons for non-adherence and to take appropriate action.

Author Contribution Statement

Conceptualization and design, Data acquisition, Data analysis and interpretation, Critical revision of the manuscript: Fatuma Hassen, Fikre Enquselassie, Aster Tsegaye, Mathewos Assefa, Ahmed Ali, Adamu Addissie, Girma Taye. Supervision and and final approval: Fatuma Hassen, Aster Tsegaye, Mathewos Assefa, Ahmed Ali, Adamu Addissie, Girma Taye.

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Ethics approval

This study was approved by Institutional Review Board of College of Health Sciences of the Addis Ababa University with protocol number 073/17/SPH.

Patient consent

Informed written consent form was signed by the participants.

Data sharing statement

Due to privacy and ethical concerns, supporting data cannot be made openly available.

Conflict of Interests

All authors declare that there is no conflict of interests regarding the publication of this paper manuscript.

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Paper- IV

Profile and association of ABO/Rh blood group with breast cancer at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: Case control study.

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Abstract

Background: ABO blood group is considered to be among the risk factors for some infectious and non-infectious diseases. Significant relationship between ABO blood group and breast cancer has been reported, though findings are inconsistent in the literature.

Objective: This study aimed to assess frequency and association of ABO blood group with breast cancer.

Methods: Case control study was conducted from May 2018 to June 2019 at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. A total of 191 breast cancer patients and 230 controls enrolled in the study. ABO and Rh types were determined for all participants fulfilling the eligibility criteria. The collected data were analyzed using SPSS version 20 statistical software. Frequency of blood group was calculated to see the distribution of each blood type. Chi-square and binary logistic regression was conducted to examine the association between blood group and breast cancer.

Results: The majority, 89 (46.6%) cases and 96, (41.7%) controls were blood group O followed by A (23.6% and 27.4%) and B (19.9% and 22.2%). Blood group AB was the least blood group, 19 (9.9%) and 20, (8.7%) of the cases and controls, respectively. Group O and Group A were higher in cases and controls, respectively, though it did not reach to statistically significant level. Besides, there was no significant association between Rh factor and breast cancer.

Conclusion: Blood group O was the predominant and AB the least blood group in both cases and controls. The study demonstrated no significant association between breast cancer and ABO/Rh blood group. Further study with large sample size is recommended in order to establish the role of ABO blood group in the prognosis of breast cancer.

Key words: Blood group, ABO/Rh, breast cancer, Ethiopia

Introduction

Breast cancer is the most commonly diagnosed cancer in women. Globally, 24.2%, of all new cancer cases identified in women is breast cancer. Breast cancer is also the leading cause of cancer death in women, which accounts 15.0% of cancer deaths [1]. In Ethiopia, breast cancer is a major public health problem as well as the most common type of diagnosed cancer in women. According to Addis Ababa City Cancer Registry, breast cancer is the leading cancer among females (33%) [2]. There are several established risk factors for breast cancer. Many of the factors known to increase the risk are not modifiable; those include age, family history, early menarche, and late menopause. However, there are controversies on the risk of breast cancer related to ABO/ Rh blood group [3]. Historically, early in the twentieth century, ABO blood group was discovered by Karl Landsteiner. Within the ABO groups, it is possible for the red cells to have either of these antigens on their surface, or both, or neither. Cells that only have the A antigen are called group A. Those that only have the B antigen are called group B. Cells that have both the A and B antigen are called group AB, and cells to lack both of A and B antigens are called O. The clinical importance of the Rh blood group system was clearly demonstrated by Levine and Stetson in 1939 when, following the delivery of a stillborn baby, a patient urgently required a blood transfusion [4]. The ‘‘ABO” and ‘‘Rhesus” blood type system is the most important basis in transfusion medicine; however, there appears to be vulnerability to some illnesses including risk of breast cancer associated with some blood genotypes [5].

Persons with Rh (-) blood group represents a very small proportion. While in Europe, America, and Australia, this rate is much higher, accounting for around 15% - 40% of the population [6].The role of ABO blood group in cancer biology has been studied by several investigators. Even though, several investigators have assessed the relationship between ABO blood group and breast cancer [7, 8]. ABO blood group system is the only system in which there is a reciprocal relationship between the antigens on the red cell and the naturally occurring antibodies in the serum [9]. Different studies conducted on the association between breast cancer and blood group are inconsistent. Studies conducted in Ankara (Turkey) and Iraq found that there was no statistically significant association between blood group and breast cancer risk [10, 11], while others reported the contrary. According to many studies, conducted in different countries including studies in Saudi Arabia, different parts of India, Yezad, Greek, and Iraq found that women with blood type A had a high risk of breast cancer while women

with blood type AB had a minimum risk [12-20]. However, study from Kuffa Iraq found that blood group O was associated with increased risk of breast cancer [21]. On the other hand a study done in India among 187 breast cancer patients and 209 controls found that blood group B was the dominant blood type in breast cancer patients, but it did not show statistically significant association [22]. Meta-analysis conducted on 9665 breast cancer patients and 244,768 controls in China, relative to blood type O, women with blood type A and AB had the same breast cancer risk with odds ratio of 1.12 and 1.042, respectively [23].

Similar with ABO blood grouping, the association of Rh blood group and breast cancer is also inconsistent. Some studies including the genome wide association studies have demonstrated an association between breast cancer and Rh type [14] while others not [11, 23, 24]. According to study done in Ethiopia, even though many studies have proven the association between ABO blood types and diseases by describing possible mechanisms, others did not. ABO may influence the risk of different diseases by different known and unknown mechanisms [25].

The percentage of the population belonging to each blood group varies with racial type [26]. Besides the controversies and uncertainties' regarding the association between ABO/Rh and breast cancer, the most likely mechanism in the progress of an association between blood types and incidence of breast cancer has not been established yet. Thus, more evidence from different population groups are needed and this study will add to the body of the literature for future studies in this issue by assessing the frequency and association of ABO blood group with breast cancer in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

Materials and Methods

Study area and population

Facility based case control study was conducted between May 2018 and June 2019 in Addis Ababa at Tikur Anbesa Specialized Hospital (TASH) Oncology Department. Tikur Anbessa Specialized Hospital (TASH), which is the largest hospital in the country with about 700 beds capacity. TASH is the main teaching hospital for both clinical and preclinical training of most disciplines. It is also an institution where specialized clinical services that are not available in

other public or private institutions are rendered to the whole nation. Until recently it was the only center for a population of over 100 million providing oncology service. TASH has 200 doctors, 379 nurses and 115 other health professionals dedicated to provide health care services [27].

Eligibility criteria

All newly diagnosed breast cancer patients, with confirmed histology result, no observable mental disorders, no history of chronic disease and aged 18 years and above were included in the study. Regarding controls, care givers who had no biological relationship with selected cases were included as controls. Since there was only one referral center for cancer treatment during the study period, the existing center (TASH) was used for the study. All voluntary and eligible cases and controls that came to Tikur Anbessa Specialized Hospital during the study period were recruited. Accordingly, a total of 421 women (191 cases and 230 controls) were participated in this study.

Data management and analysis

Informed consent was obtained from each study participant prior to data collection. Participants were interviewed by experienced and trained nurses in order to get socio demographic data using pretested questionnaire. Breast physical examination was conducted by oncology residents in order to select eligible controls. Finally 2-3 milliliter of venous blood was collected from the control groups for ABO/Rh Blood grouping. ABO/Rh blood grouping was done using slide agglutination method using commercially available anti sera (anti-A, anti-B, Anti-D). For breast cancer cases their blood group was recorded from their cards. Data entry and analysis was done using SPSS Software, version 20. Chi-square test and binary logistic regression analysis was conducted to see the association between breast cancer and blood group. P value less than 0.05 were considered as statistically significant.

Data Quality Assurance and Ethical consideration

Data collection tools were prepared in English and translated to the local language in order to facilitate understanding by study participants. Data collection tools were pretested in 5% of breast cancer patients not included in the study. Daily supervision was made on all questionnaires collected each day. ABO/Rh typing was carried out by experienced laboratory personnel following standard operating procedures. This study was approved by the School of

Public Health Research Ethical Review Committee, and by the Institutional Review Board of the College of Health Sciences of the Addis Ababa University. Written consent was obtained from each of the respondents after the purpose of the study was explained. During breast physical examination for screening of controls, participants who had breast mass were consulted by physicians and their results were provided in order to get early diagnosis and treatment. Confidentiality and privacy were maintained throughout the study.

Results

Socio demographic characteristics of study participants

In this study, a total of 421 study participants (191 cases and 230 controls) were enrolled (Table 1). Regarding residence, majority, 131, (68.6%) of cases and 174, (75.7%) of controls were urban residents. The mean age was 43.06 $\pm$ 12.3 and 39.44 $\pm$ 11.0 years for cases and controls respectively. Regarding marital status, 173, (90.6%) of cases and 201, (87.4%) of controls were married. Nearly half, 84, (44%) of cases were illiterate, while only 34, (14.8%) of controls were illiterate. Majority, 130, (69%) of cases and nearly half 99, (43%) of controls were unemployed (Table 1).

Insert Table 1 here

Frequency of ABO/Rh blood group of study participants

In this study, the majority, 89 (46.6%) of cases and 96, (41.7%) of the controls had O blood group followed by A blood group and B blood group (Table 2). Blood group AB was the least blood group, 19 (9.9%) and 20, (8.7%) among cases and controls, respectively. The frequency of ABO blood group among both cases and controls was in order of O> A >B > AB. There was no significant association between ABO blood group and breast cancer (Table 2).

Insert Table 2 here

‘‘Rhesus” (Rh) Blood group

In this study majority of study participants 92.9 % (both cases and controls), were Rh positive while 7.1% were Rh negative. There was no significant difference between cases and controls in Rh positivity; 117(92.7%) of case and 214, (93%) of the controls were Rh positive. Thus, as

indicated in Table 3, there was no significant association between Rh blood group and breast cancer, (P= 0.882) (Table 3).

Insert Table 3 here

As shown in Figure 1, the frequency of ABO/Rh blood group was almost the same among cases and controls when combining ABO and Rh types. Majority, 86, (45%) of cases and 91 (39.6%) controls were O+. It is also found that 37, (19.4%) of cases and 58, (25.2%) of controls were A+. A blood group is found to be higher among control groups; however the difference was not statistically significant. Similarly 37, (19.4%) of cases and 47, (20.4%) of controls were B+. On the other hand only 3, (1.6%) of cases and 5, (2%) of controls were O negative. However, AB- is the least blood type for both groups (about 1%). (Figure 1)

Insert Figure 1 here

Discussion

Female breast cancer is among the top three cancers in terms of incidence. About one in 4 of all new cancer cases diagnosed in women worldwide are breast cancer. Breast cancer is also the leading cause of cancer death in women (15.0%), and among the top five in terms of mortality [1]. The ABO-Rh Blood group has been shown to serves as a predictor of survival in breast cancer. A study done in Turkey revealed that overall and disease-free survival times were higher in breast cancer patients with A and O blood groups when compared to those with other blood groups. It was seen that A and O blood groups have good prognostic value in patients with breast cancer [28].

The current study aimed to assess ABO blood group frequency and association between ABO-Rh type and breast cancer by studying 191 cases and 230 healthy controls. Blood group O was the predominant and AB the least frequent blood types among breast cancer patients as well as healthy controls. In general the distribution of ABO blood group was O> A >B > AB, which was comparable with study conducted in Tanzania, which reported blood group was O (52.3%) and the least common was AB blood group (3.18%) [29]. The current study finding was also supported by other studies conducted in Uganda and Nigeria [30,31]. Regardless of breast cancer status, the finding of this study was also comparable with studies done in different parts of Ethiopia like, Arbaminch, 42.1% O and 4.3% AB, blood group [32], Gambella 41.2% group O

and 3.34 group AB [33], Debre tabor, 39.6% O and 7% AB, [34] and Silte zone, 43.08% O and 5.44% AB [35]. However these frequencies have certain variation among different ethnic groups and geographical location for example, as indicated in the previous study from Gambella, A blood group was the predominant (44.07%) blood group among highlanders, whereas O was the most frequent (50.42%) blood group among Nilotic natives [33].

It was also found that 7.1% of the study participants were Rh negative. This finding is comparable with other studies in Ethiopia which reported 7-8% of study participants were Rh negative [32, 34, 35]. This finding was also supported by studies from Iran (8.9%) [36] and Colombia (8.7%) [37]. On the other hand, lower frequencies of Rh- blood type was reported from Tanzania (2.3%) [29] and Uganda (2.0%) [30]. This difference could be due to differences in ethnic group and geographical differences.

Study from China found that ABO and Rh blood distribution was significantly different among nine ethnic groups [38]. The issue of ethnic differences has also been reinforced by a study from Gambella, west Ethiopia. The study found that 19.37% of study participants were Rh negative, a frequency which is much higher than what was reported so far for Ethiopia [33].

Blood types have been reported to be associated with several diseases including breast cancer. Although findings are inconsistent and unclear, there are several studies conducted on the association of blood type and the risk of breast cancer. Some studies revealed that, there is no association between ABO blood type and breast cancer. However other studies found that there is high risk of breast cancer among women with 'A' blood type. The current study, found that there was no significant association between ABO blood types and breast cancer incidence. This finding was supported by different studies conducted in Turkey, Iraq and India, which reported that even though there was no significant difference between cases and controls blood group B was found to be higher in breast cancer patients [10, 24, 25].

In contrast, many studies demonstrated a higher risk of breast cancer among study participants who had "A" blood type. There are many studies which have found that the risk of breast cancer is significantly higher among women who had A blood group and there is minimum risk among women who had AB blood group, [12 -20]. On the other hand, a study from Iraq showed that O+ blood group was positively associated with the risk of breast cancer [21].

This study also found that Rh type had no significant association with breast cancer risk. This finding is supported by similar studies done in Iran, China and India, [11, 23, 25]. However, studies from Saudi Arabia found that breast cancer is more common in patients with Rh positive blood groups [11]. This difference could be due to study design and sample size of different studies, since the Saudi study was systematic review. It could also be difference in ethnic group and geographical location.

In conclusion, this study found that the majority of cases and controls had O positive blood groups. Similarly, 117(92.7%) of case and 214, (93%) controls were Rh positive. Even though some previous studies have reported significant associations between ABO/Rh blood group and breast cancer risk, our study adds to the body of evidence that demonstrated no significant association between ABO/Rh blood group and breast cancer risk. Since there are inconsistencies on the association between ABO blood group and breast cancer risk and this finding does not show significant association, further studies should be done with large sample size, different geographical location and ethnic group in order to establish the role of ABO blood group in the prognosis of breast cancer.

Declaration

Funding

This study was supported by Addis Ababa University and principal investigator. The university had no role in the study design, data collection and data analysis, decision to publish and manuscript preparation.

Conflict of Interests:

All authors declare that there is no conflict of interests regarding the publication of this paper manuscript

Availability of data and material

- The datasets generated and/or analyzed during the current study are not publicly available due to individual privacy but are available from the corresponding author on reasonable request.

Authors' Contribution:

- **Conceptualization and design:** Fatuma Hassen, Fikre Enquselassie, Aster Tsegaye, Mathewos Assefa , Ahmed Ali, Adamu Addissie , Girma Taye.
- **Data acquisition:** Fatuma Hassen, Fikre Enquselassie, Aster Tsegaye, Mathewos Assefa , Ahmed Ali, Adamu Addissie , Girma Taye.
- **Data analysis and interpretation:** Fatuma Hassen, Fikre Enquselassie, Aster Tsegaye, Mathewos Assefa , Ahmed Ali, Adamu Addissie , Girma Taye.
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- **Supervision:** Fatuma Hassen, Aster Tsegaye, Mathewos Assefa , Ahmed Ali, Adamu Addissie , Girma Taye.
- **Final approval:** Fatuma Hassen, Aster Tsegaye, Mathewos Assefa , Ahmed Ali, Adamu Addissie , Girma Taye.

Ethics approval and consent to participate

- This study was approved by Institutional Review Board of College of Health Sciences of the Addis Ababa University. Informed written consent form was signed by the participants. Confidentiality was highly maintained throughout this study.

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Table 1 Socio demographic characteristics of study participants at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2020, (n=421)

Variables	Case (n=191) N (%)	Control (n=230) N (%)
Residence		
Rural	60 (31.4)	56 (24.3)
Urban	131 (68.6)	174 (75.7)
Age group (years)		
<40	89(46.6)	136 (59.1)
40–49	46 (24.1)	45 (19.5)
50-59	32(16.7)	36(15.7)
60 and above	24 (12.6)	13 (5.7)
Mean ± SD) (year)	43.06 ± 12.3	39.44 ± 11.0
Marital status		
Ever Married	173(90.6)	201(87.4)
Never married	18(9.4)	29(12.6)
Education level		
Literate	107(56.0)	196(85.2)
Illiterate	84(44.0)	34(14.8)
Occupation		
Employed	61(31.9)	131(57)
Unemployed	130(69.6)	99(43.0)

Table 2. Distribution of ABO Blood groups of breast cancer cases and controls at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2020. (n=421)

Blood group	Case		Control		P- Value
	No	%	No	%	
A	45	23.6	63	27.4	Ref
B	38	19.9	51	22.2	0.884
AB	19	9.9	20	8.7	0.447
O	89	46.6	96	41.7	0.286
Total	**191**	**100**	**230**	**100**	

Table 3. Frequency of Rh Blood groups of breast cancer cases and controls at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2020. (n=421)

Rh factor	Case		Control		P value
	No	%	No	%	
Rh positive	177	92.7	214	93.0	0.882
Rh negative	14	7.3	16	7.0	
Total	**191**	**100**	**230**	**100**	

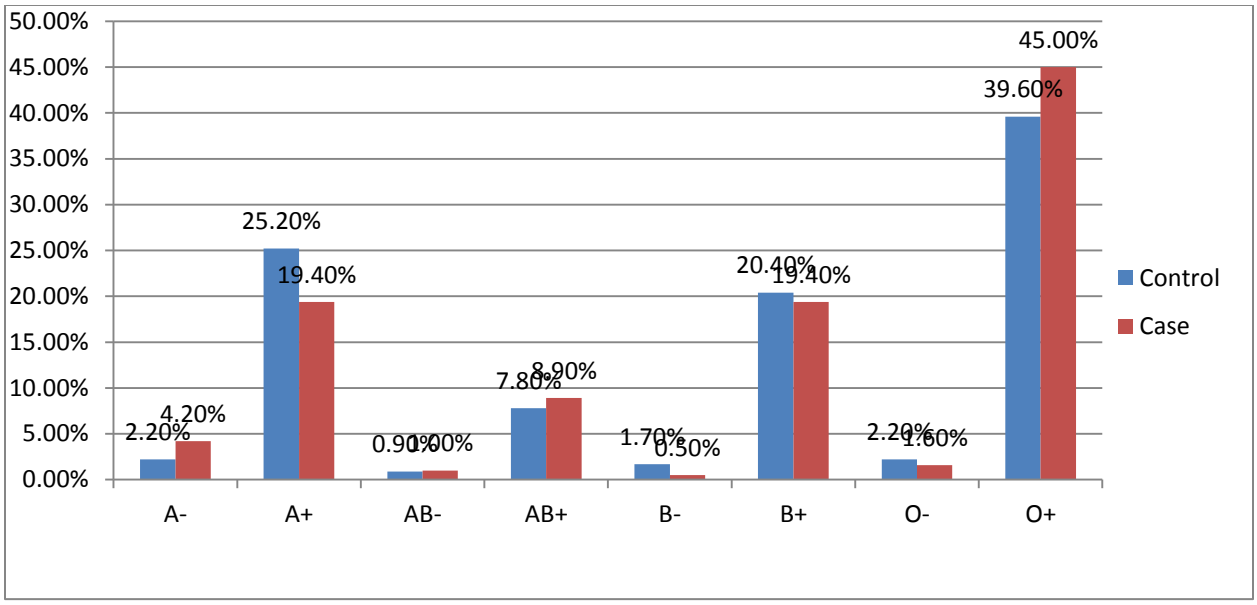

Figure 1. ABO/Rh blood groups frequencies of breast cancer cases and controls at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2020, (n=421).

Paper - V

Survival of breast cancer patients treated at Tikur Anbessa specialized and Teaching Hospital, Addis Ababa Ethiopia.

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Abstract

Purpose: Globally, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths in women. The purpose of this study was to determine survival of breast cancer patients and associated factors.

Methods: This study was done among breast cancer patients treated at oncology Center of Tikur Anbessa Hospital, Ababa, Ethiopia. Clinical data were collected from patient files. Median age at diagnosis and Interquartile range (IQR) was calculated. Based on life table analysis one, three, five and 10 years overall survival rates were calculated. Median survival estimates was obtained using Kaplan-Meier survival analysis method. Survival curves were compared using the Log-Rank statistic. Bivariate and multivariate analysis was performed using Cox's proportional hazards model.

Results: Our study included a total of 402 patients followed over 10 years. Median age at diagnosis of patients was 43.4[35-50] years. The median follow up time was 58.3 months while the total person year was 22,998 months. By the end of follow up, 233, (58%) of patients were dead. The one, two, three, five and ten year survival rates were 85, 75, 62, 50 and 34%, respectively. Based on multivariate cox regression analysis, more sever stage at diagnosis (HR=3.84; (95% CI 2.00-7.35, P< 0.001), cancer metastasizing 1.79(95% CI, 1.13-2.83, P = 0.012) were significantly associated with an increased risk of death.

Conclusion: Our study indicated relatively poor survival rate which was associated with late stage diagnosis and metastasizing cancer. Strengthening public awareness and mass screening is needed in order to enhance early screening and initiation of treatment to reduce advanced stage of breast cancer.

Key words: *Breast cancer, survival, Kaplan-Meier, cox regression.*

Introduction

Breast cancer is the most commonly diagnosed cancer in women. Globally, 24.2%, of all new cancer cases identified in women is breast cancer. Breast cancer is also the leading cause of cancer death in women, which accounts for 15.0% of cancer deaths [1]. Survival is extremely determined by stage of the disease and tumor size; for example, 5-year relative survival is 99% for localized disease, 85% for regional disease, and 26% for distant-stage disease [2]. Regarding tumor size, among women with regional disease, the 5-year relative survival is 95% for tumors ≤2.0 cm, 84% for tumors 2.1-5.0 cm and 70% for tumors greater than 5.0 cm [2]. A study conducted in Canada, showed that the 5-year overall survival rates were 43.2% for those who refused standard treatments [3]. A study conducted in Spain among 369 breast cancer patients also found that differences in survival at early stages were statistically significant [4].

Other study conducted in the Netherlands and Ireland showed that five-year relative survival was 88.8% and 82.9%, respectively [5]. Study conducted in Vietnam, showed that the overall survival rate was estimated to be 0.94, 0.83, and 0.74 at 1, 3, and 5 years, respectively [6]. Relatively lower survival rate was reported from Malaysia with an overall 5-year survival rate of 49.4% and median survival time of 68.1 months. In addition, overall observed survival rates at 1, 3 and 5 years were 70.8%, 56.9% and 49.4%, respectively [7]. Another study from Iran also reported a one-, two-, three-, five-, and ten-year breast cancer-specific survival rates were 0.92, 0.88, 0.84, 0.77, and 0.65, respectively [8]. The five year survival study from Pakistan revealed a median survival of 39 months and stage based median survival of 48, 34, 26 and 14 months for stage I, II, III, and IV patients, respectively [9].

A study conducted at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia from 1995-99 found that majority of cases, (60.2%) were at stages III and IV disease [10]. Short-term clinical disease-free or improved survival was observed in cases of stage II disease regardless of age and in those that received multimodality therapy. Only 4 cases had at least 5 years of survival [10]. Very low 5-years survival rate during advanced stage was recorded among 482 women investigated from rural Ethiopia [11].

Tikur Anbessa Specialized Hospital was the only and still the main tertiary care referral and teaching hospital where oncologic patients are referred from all over the country. In recent years there is an effort by the Federal Ministry of Health of Ethiopia to expand the service to other teaching hospitals as the unmet need is so huge. Updated information on factors predicting long term survival rate can guide decisions as well as support by the ministry. This study is the first to provide such evidence for informing decision making.

Patients and methods

Study setting

This study was conducted in Addis Ababa at Tikur Anbessa Specialized Hospital (TASH) Oncology Department. The Oncology Center is the only institution which provides radiotherapy service in Ethiopia. The Hospital has one CT scanner and one MRI scanner. The Hospital has 600 beds, of which 18 are allocated for cancer treatment. Of the 201 physicians in the hospital only four are medical oncologists, four are radiotherapists, two are surgical oncologists and one is a pediatric oncologist. Three palliative pain specialists also work at the Hospital. Only 26 of the TASH's 627 nurses are dedicated oncology nurses (12).

Study design and population

Retrospective cohort study design was utilized to determine survival of breast cancer patients. The study was conducted from February 2019 to June 2021 by using data of breast cancer patients diagnosed from September 2010 to August 2014. A total of 402 women patients with complete records, have at least two follow up visits, patients 18 years and above were included in this study. On the other hand, those patients without phone number in their file and male patients were excluded. During the follow up period women with unknown outcome (patents with death or alive) were excluded from the analysis.

Data collection, analysis and management

Structured checklist was prepared based on pre-determined patient from their records. Data were collected by trained and experienced oncology residents working at TASH, Oncology Department. In addition, phone call had made to confirm whether the patient alive or death. The patient follow up was conducted by including all eligible patients and data was collected from the patient records. After this, phone call had made and those patients whose phone did not

respond after repeated call were excluded from the analysis. The entire data collection process was supervised by the principal investigator. Data was entered using EPI-INFO statistical software and analyzed by Statistical Package for Social Science (SPSS) version 20 Software. Then, descriptive analysis was made to assess socio-demographic characteristics. Survival was calculated as the time difference in months, between date of diagnosis and date of death during the follow-up period. Patients who remained alive until the last follow up were censored. In this case, the censor date for patients who remained alive was the date of phone call which had confirmed the status of the patient. Based on life table analysis one, three, five and ten year overall survival was calculated. Median survival estimates were obtained using Kaplan-Meier survival analysis method. Survival curves were compared, using the Log-Rank statistic. Bivariate and multivariate analysis was performed using Cox's proportional hazards model.

Data Quality Assurance

To ensure data quality, data were collected by trained and experienced oncology residents. The principal investigator made daily supervision was made on all collected data.

Ethical considerations

Ethical approval was obtained from College of Health Sciences Institutional Review Board of Addis Ababa University with protocol number 073/17/SPH. Waiver of consent was secured from the college IRB to extract secondary data from patients' records. Confidentiality of information was maintained throughout the study.

Results

Socio demographic characteristics

A total of 402 patients were collected from patients with up to 10 years of follow-up. The median follow up was 58.26 months with the range of (1-120) months. The majority of patients, 203, (50.5%) were from Addis Ababa (Table 1). Majority, 109, (39.8%) of patients were less than 40 years, with median age of 43.4 years at time of diagnosis. The median age was 43.4[35-50] years. At the end of follow up, 169, (42%) patients were alive (censored) and 233, (58%) patients were dead (Table 1).

Insert Table 1 here

Clinical and tumor related characteristics

Almost half, 200 (49.8%) of study participants had left side tumor. Two hundred six patients (51.2%) were in stage III, followed by 100 (24.9%) in stage IV. However, very few, 11 (2.7%) of the patients were in stage I (Figure 1)

Insert Figure 1 here

In this study nearly half, 200 (49.8 %) of the study participants were treated with left side tumor. Similarly, majority, 206, (51.2%) of the study participants were with stage III tumor at time of diagnosis. Majority, 332(82.6) of patients were diagnosed with ductal carcinoma with undifferentiated tumor grade being detected in 139(34.6) patients. Besides, 111, (27.6) of study participants had metastasis to distal organ at diagnosis, of which 42 (37.8) had lung metastasis. The mean tumor size was 4.92 $\pm$ 4.22 cm. Majority, of study participants 131, (32.6%) had tumor size greater than 5 cm, of which 90, (68.7%) had died. Primary treatment was surgery in 317, (78.9%) of patients, followed by chemotherapy, 69, (17.2%). In general, 362, (90.5%), 185(46.0%) of patients were treated with chemotherapy and hormone therapy, respectively (Table 2).

Insert Table 2 here

Survival status of breast cancer patients

Survival status of breast cancer patients

This study also revealed that the median follow up time was 52.8 months. Using Kaplan Meier analysis the overall median survival time was 61.96 (95% CI: 49.71-74.41) months. There was no significant difference in median survival of patients residing in or outside Addis Ababa (63.90, 95% CI, 45.25-82.54 and 55.50, 95% CI: 43.10 to 67.89), P= 0.431). The one, two, and three year survival rates were 85%, 75%, and 62%, respectively. Whereas the five year survival rates was 50%. Based on the result of Kaplan Meier analysis there was a highly significant survival difference among women based on stages of disease. As compared to stage I, stage IV patients have a lower chance of survival, with median survival of 21.80 (95% CI 13.75-29.84, P

= 0.001) months (figure 5). Women who had poorly differentiated or undifferentiated nuclear grade tumors have also significantly lower chances of survival. Compared to patients with tumor size less than 2cm, patients with tumor size greater than 5 cm had significantly poor median survival (43.73, 95% CI, 32.11-55.35, P < 0.001). Better median survival, 81.80(66.15-97.45, P < 0.001)) months, had seen among patients who were primarily treated with surgery because patients treated primarily are in the early stage and receive additional therapy as well- chemo, radio, or hormone therapy. Significantly low median survival was also recorded in patients who received neither chemotherapy nor radiotherapy (Table 3).

Insert Table 3 here

Kaplan-Meier Survival analysis

Based on the result of Kaplan-Meier Survival analysis, median survival and survival probability was calculated. The result showed that for stage IV patient's median survival time was 21.80 (95% CI 13.75-29.84) months. Which was significantly lower (P < 0.001) as compared to patients with stage I and II. It is known that patients diagnosed at an advanced stage have worse survival (Figure 2).

Insert Figure 2 here

On the other hand, the finding also showed that , based on the result of Kaplan-Meier Survival analysis, there was significantly better median survival, 81.80, 95% CI, (66.15-97.45),) months, among patients who had been primarily treated with surgery. Log rank, P <0.001 as compared to other forms of treatment (Figure 3).

Insert Figure 3 here

As indicated in the above section, 27.6 % of women had metastasized tumor. Based on the result of Kaplan-Meier Survival analysis, compared to patients without metastasized tumor, patients with metastasized tumor had significantly lower median survival 29.43 95% CI (19.85-39.0) months, log rank, P <0.001) (Figure 4).

Insert Figure 4 here

Bivariate and multivariate cox regression analysis

According to bivariate cox regression analysis there was no significant difference in survival of patients by age groups, types of tumors histology and tumor size (P >0.05). However being in stage four had 7.65 times higher risk of death with HR= 7.65 (4.8-12.51, P< 0.001) as compared with patients with stage one. Patients with higher grade (grade III) or undifferentiated tumor had higher risk of death as compared to those with lower grade tumor (grade I). Patients with undifferentiated tumor had 2.37 times higher death (HR=2.37; 95% CI: (1.48-3.82 P < 0.001). Besides, there was significant difference in survival by tumor metastasis status of patients at time of diagnosis. According to type of treatment, patients who were not treated with surgery had significantly worse survival (HR=2.85, 95% CI (2.15- 3.79).

Based on multivariate cox regression analysis, stage at diagnosis, metastasis status and treatment status of patients remained significantly associated with worse survival. Patients with stage four compared with stage one and stage two (HR=5.27; 95% CI :1.96-7.14.18, P< 0.0001), and patients with metastasized tumor compared to those without metastasized tumor (2.01; 95% CI: 1.13-3.56, P = 0.018) had a higher death hazard. However, the protective role of surgery as treatment did not reach statistical significance (HR; 1.38; 95% CI : 0.809-2.35, P=0.238). On the other hand, compared to those who were treated, women who were not treated with hormone had 1.69 times higher death hazard (HR; 1.69; 95% CI, 1.14-2.51, P=0.010). There is weak evidence to suggest women who were not treated with radiation had higher death hazard compared to women with radiation (HR; 1.47; 95% CI: 0.943-2.29,P=0.089) (Table 4).

Insert Table 4 here

Discussion

This study aimed to analyze survival rate of 402 breast cancer patients who had up to 10 years follow up at the oncology center of a tertiary care referral and teaching hospital in Ethiopia. Of them, 233, (58%) died and the remaining 169, (42%) were censored at the end of the study. Almost half of the patients were residing in Addis Ababa, which was comparable with an earlier report [13]. Consistent with previous studies from Ethiopia, younger age group of less than 40 years were more affected [14-16]. Relatively older age groups are affected according to other studies; the median ages were 53 and 45 years in two different studies conducted in Sudan [17,

18] while in the study done in Pakistan majority of the participants were found below 50 years [19]. Whereas, in studies from Iran [20] and Mexico [21] breast cancer patients were predominantly older patients who are aged above 50 years. This difference could be due to the demographic characteristics of the Ethiopian population which is predominantly young age as compared to other countries.

The study revealed almost half 200 (49.8%) of patents had the tumor in the left side, which was consistent with a study done in Nigeria which identified 50.3% of the participants had left side breast tumor [22]. The finding of over half (51.2%) of patients being in stage III at diagnosis, was comparable with a study done in Sudan (45.9%) [17] as well as in Nigeria (55.3%) [22] but higher than studies done in Pakistan, Latin America and the Caribbean. This could be due to better treatment in these countries and majority of patients seeking care at early stage of the disease so that occurrence of advanced stage might be decreased [24 , 23]. The other explanation for Ethiopian patients presenting at advanced stage of cancer could be due to patient delay as a result of illiteracy, lack of health care access, financial constraints, inadequate diagnostic facilities, poorly structured referral and sought traditional healers as described by different studies done in Ethiopia [25-27].

In this study majority, 332(82.6%) of patients were diagnosed with ductal carcinoma which was comparable with previous study done in Ethiopia [13] as well as in Nigeria (89.2%) [22]. While slightly higher than the report from Sudan (69.2%) [18]. Regarding tumor grade, consistent with previous study from Ethiopia, majority of study participants, 139(34.6) had undifferentiated grade [13].

The finding of metastasized tumor to distal organ at diagnosis in 27.6% patients of the current study was comparable to the study done in Nigeria (28.5%) [22]. The mean tumor size was 4.92 $\pm$ 4.22 cm which was comparable to an earlier study done in Ethiopia [13]. For majority, 317, (78.9%) of patients, primary treatment was surgery; this finding was lower than study done in Addis Ababa revealed that modified radical mastectomy was done for 94.6 of patients. The difference could be that some women might be operated after some forms of treatment such as chemotherapy [13]. The number of women receiving chemotherapy between the two studies was comparable (90.5% versus 87.5% in the earlier study from Ethiopia) [13].

In this study the median follow-up time was 52.8 months. Based on life table analysis, the one-, two-, three-, five-, and ten-year survival was 85, 75, 62, 50 and 34%, respectively. Though consistent with the study done in Addis Ababa , which reported 74% survival after 2 years and 46% after 5 years [13], our finding was lower than the one-, two-, three-, five-, and ten-year breast cancer-specific respective survival rate of 0.92, 0.88, 0.84, 0.77, and 0.65 reported from Iran [8]. The likely explanation could be the majority of patients in the current study were treated with grade two tumor which might have impacted their survival. In this study, younger women had worse survival as compared with older women. This study was not supported by similar study done in Iran in which older individuals (≥50 years) had significantly worse survival [24]. Another study from Poland also indicated that older women with breast cancer are treated similarly to younger patients, but have significantly worse chances to survive [28]. This difference could be due to large percentage of our study participants were found to be in younger age as compared with other similar studies.

In addition, compared to those with grade one tumor, women who had grade three or undifferentiated tumors had lower chance of survival, which agrees well with previous study done in Addis Ababa [13]. Based on bivariate Cox regression there was no significant difference in survival by surgical treatment status of patients. This finding was not supported by study done in Riyadh, Saudi Arabia where the 5-year survival rate for Surgery group was 34% compared with 14% for the non-surgery group [29]. This difference could be due to lack of health care access leading to more advanced disease until patients undergo surgery.

The current study also detected worsened survival in women who did not receive hormone therapy. Our finding was supported by a study done in Mexico which revealed that women who did not receive endocrine therapy (HR 2.0; 95% CI 1.0–4.0) had an increased risk of breast cancer death relative to those who did receive these therapies [29].

Finally, multivariable Cox regression analysis revealed stage of disease at diagnosis, metastasis status and treatment status were significantly associated with survival. Patients with stages three and four had significantly worse survival. Similarly, patients with metastasis had 2.01 times worse survival. This finding is comparable with study done in China which reported that metastasized cancer resulted significantly poorer breast cancer specific survival (HR, 1.99; 95%

CI, 1.43-2.78; P < .001) and overall survival (HR, 1.79; 95% CI, 1.35-2.38; P < .001). In addition patients who did not receive hormone therapy had significantly lower survival as compared with patents who had received these treatments [30]. In general, our study indicated that the overall 5 year survival of breast cancer patients was lower even as compared with the five year overall survival our neighbor Sudan (79%) and Egypt (68%) [31, 32]. This lower survival rate of patients attributed with large number of breast cancer patients were treated at advanced (stage III and stage IV) stage of disease. Therefore, awareness creation, early screening, early diagnosis and improved treatment should be the most important strategy in order to minimize the risk of advanced breast cancer and improve overall survival of patients.

Limitation

Significant number of records/study participants were excluded from the analysis due to lack of outcome status of patients. This probably may overestimate the survival of our study participants, because those patients who we could not be reached through phone were more likely to die.

Conclusion

At the end of the follow-up of the 402 patients included in the analysis, 169, (42%) patients were alive (censored) and 233, (58%) of patients were dead. Based on the result of Kaplan Meier analysis the overall median survival time was 61.96 (95% CI: 49.71-74.41) months. The overall one, two, three, 5 year and 10 survival proportions were 85, 75, 62, 50 and 34% respectively. In general, this study found that survival was relatively poor and is associated with diagnosis with late stage disease. Based on multivariate cox regression, significantly lower survival was associated with advanced stages (stage III and stage IV) and having metastasized tumor. Therefore, mass awareness creation campaign should be strengthened in order to expand early screening; stage diagnosis and initiation of treatment to reduce advanced stage of disease and to maximize survival status of breast cancer patients.

Declaration

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Conflict of Interests:

- All authors declare that there is no conflict of interests regarding the publication of this paper manuscript.

Data Availability statement: Due to privacy and ethical concerns, supporting data cannot be made openly available.

Authors' Contribution:

- **Conceptualization and design:** Fatuma Hassen, Fikre Enquselassie, Aster Tsegaye, Mathewos Assefa , Ahmed Ali, Adamu Addissie , Girma Taye.
- **Data acquisition:** Fatuma Hassen, Fikre Enquselassie, Aster Tsegaye, Mathewos Assefa , Ahmed Ali, Adamu Addissie , Girma Taye.
- **Data analysis and interpretation:** Fatuma Hassen, Fikre Enquselassie, Aster Tsegaye, Mathewos Assefa , Ahmed Ali, Adamu Addissie , Girma Taye.
- **Critical revision of the manuscript:** Fatuma Hassen, Aster Tsegaye, Mathewos Assefa , Ahmed Ali, Adamu Addissie , Girma Taye.
- **Supervision:** Fatuma Hassen, Fikre Enquselassie, Aster Tsegaye, Mathewos Assefa , Ahmed Ali, Adamu Addissie , Girma Taye.

- **Final approval:** Fatuma Hassen, Aster Tsegaye, Mathewos Assefa , Ahmed Ali, Adamu Addissie , Girma Taye.

Ethics approval: This study was approved by Institutional Review Board of College of Health Sciences of the Addis Ababa University.

Patient consent: Informed written consent form was signed by the participants.

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Table1. Socio demographic characteristics of breast cancer patients attending treatment center at Tikur Anbesa Specialized Hospital (N=402), 2021.

Variables	**Patient status**		**Total N (%)**
Residence	**Censored N (%)**	**Death N (%)**	
Addis Ababa	91 (44.8)	112 (55.2)	203(50.5)
Oromia	38 (38.0)	62 (62.0)	100 (24.9))
Amhara	15(31.9)	32 (68.1)	47 (11.7)
SNNP	9(34.6)	17(65.4)	26 (6.5)
Tigray	6(42.9)	8 (57.1)	14(3.5)
Other	7(87.5)	1 (12.5)	8(3.0)
Age at diagnosis			
Less than 40	64 (40.3)	95(59.7)	159(39.8)
40-49	45 (41.3)	64(58.7)	109 (27.3)
50-59	43 (47.3)	48(52.7)	91(22.6)
60 and above	15(37.5)	25(62.5)	40(10.0)
Median age at diagnosis: 43.4[35-50] years			

Table 2. Clinical and tumor-related characteristics of breast cancer patients attending treatment center at Tikur Anbesa Specialized Hospital (N=402)

Variables	**Patient status**		**Total N (%)**
	Censored N (%)	**Death N (%)**	
Tumor side			
Right	69(37.5)	115(62.5)	184(45.8)
Left	93(46.5)	107(53.5)	200(49.8)
Bilateral	1(14.3)	6(85.7)	7(1.7)
Unknown	6(54.5)	5(45.5)	11(2.7)
Stage			
I	9(81.8)	2(18.2)	11 (2.7)
II	55(75.3)	18(24.7)	73(18.2)
III	86(41.7)	120(58.3)	206(51.2)
IV	15(15.3)	83(84.7)	98(24.3)
Unknown	4(28.6)	10(71.4)	14(3.5)
Histology			
Ductal	137(41.3)	195(58.7)	332(82.6)
Lobular	11(57.9)	8(42.1)	19(4.7)
Other/unspecified	21(41.2)	30(58.8)	51(12.7)
Grade			
Grade I	37(63.8)	21(36.2)	58(14.4)
Grade II	54(49.4)	83(60.6)	137(34.1)
Grade III	28(41.2)	40(58.8)	68(16.9)
Undifferentiated	50(36.0)	89(64.0)	139(34.6)
Recurrence			
No	142 (44.4)	178 (55.6)	320(81.2)
Yes	24 (32.4)	50 (67.6)	74 (18.8)
Metastasis to distal organ			
No	152(52.2)	139(47.8)	291(72.4)

Yes	17(15.3)	94(84.71)	111(27.6)
Tumor size			
< 2cm	20 (60.6)	13 (39.4)	33(8.2)
2-5 cm	72(50.7)	70(49.3)	142 (35.3)
> 5	41 (31.3)	90 (68.7)	131 (32.6)
Mean tumor size: 4.92 ± 4.22 cm			
Primary treatment			
Surgery	153(48.3)	164(51.7)	317 (78.9)
Chemotherapy	15(21.7)	54 (78.3)	69 (17.2)
Other	1 (6.3)	15(93.7)	16 (4.0)
Chemotherapy			
Yes	158 (43.6)	204 (56.4)	362(90.5)
No	9 (52.9)	8 (47.1)	17 (4.3)
Unknown	2 (8,7)	21(91.3)	23(5.7)
Hormone			
Yes	92(49.7)	93(50.3)	185(46.0)
No	41(37.6)	68(62.4)	109(27.1)
Unknown	36(33.3)	72(66.7)	108(26.8)
Radiation			
Yes	70(54.7)	58(45.3)	128(31.8)
No	46(33.3)	92(66.7)	13834.3)
Unknown	53(39.0)	83(61.0)	136(33.8)

Table 3. Median survival time and log rank testes based on different characteristics of breast cancer patients attending treatment center at Tikur Anbesa Specialized Hospital (N=402), 2021.

Variable	Median survival time in months (95% CI)	Log rank test
Place of residence		
Addis Ababa	63.90(45.25-82.55)	0.431
Outside Addis Ababa	55.50(43.10- 67.89)	
Age (years)		
Less than 40	55.50(41.71-69.28)	0.764
40-59	66.90(50,14--83.66)	
60 and above	57.23(44.68-69.78)	
Recurrence		
No	66.90(50.63-83.16)	0.063
Yes	49.60(38.16-61.03)	
Tumor size (Cm)		
Less than 2	79.67(37.55121.77)	0.001
2-5	92.50(75.05-19.94)	
Greater than 5	43.73(32.11-55.35))	
Primary treatment		
Surgery	81.98(66.15-97.45)	0.001
Chemotherapy	25.73(18.19-33.21)	
Other	11.00(3.22-18.77)	

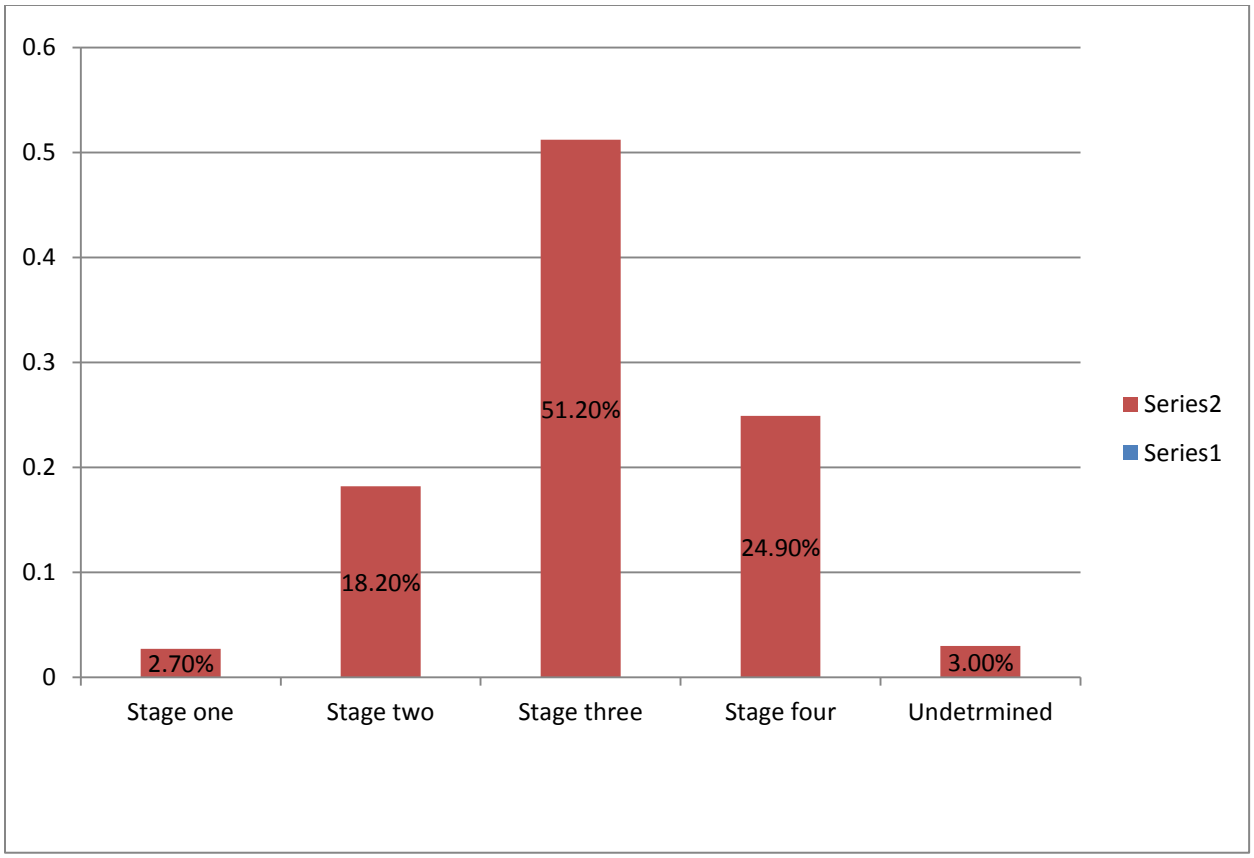

Figure 1. Distribution of patients according to stage of tumor at diagnosis at Tikur Anbesa Specialized Hospital (N=402), 2021.

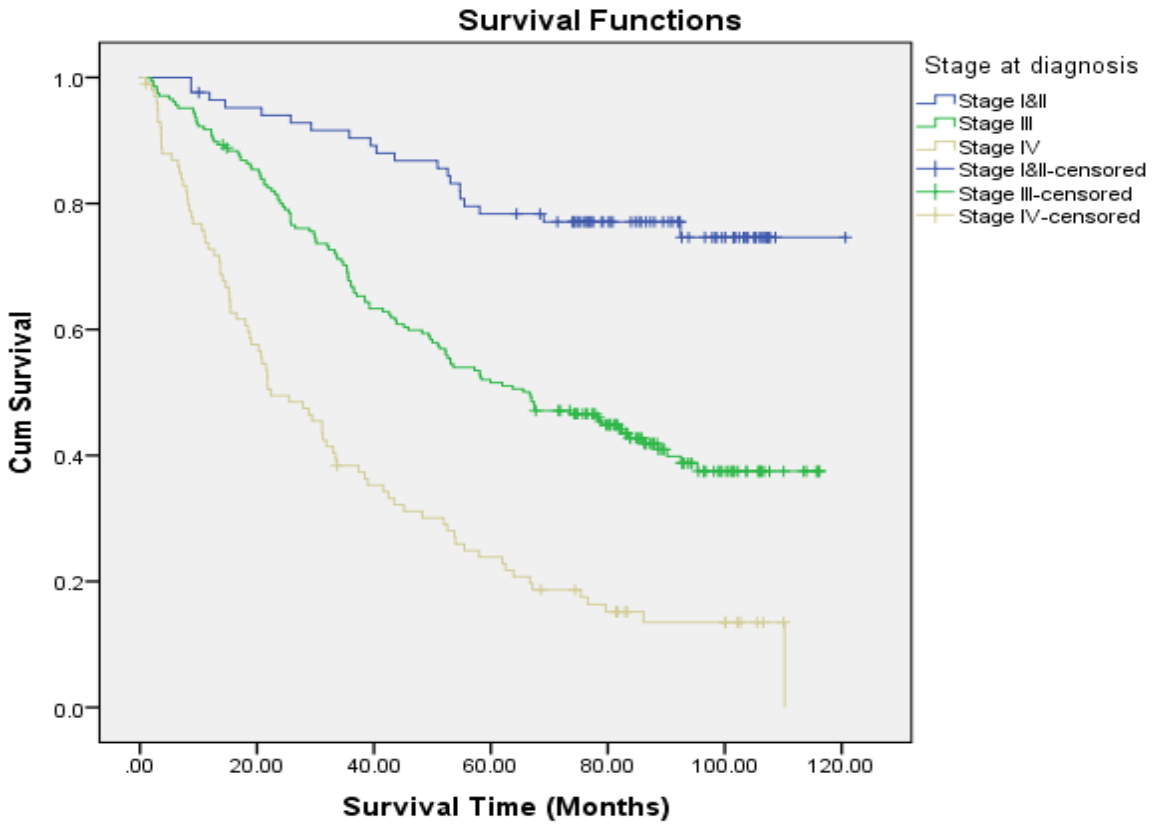

Figure 2. Stage at diagnosis and overall survival rate of breast cancer patient's treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, (N=402), 2021.

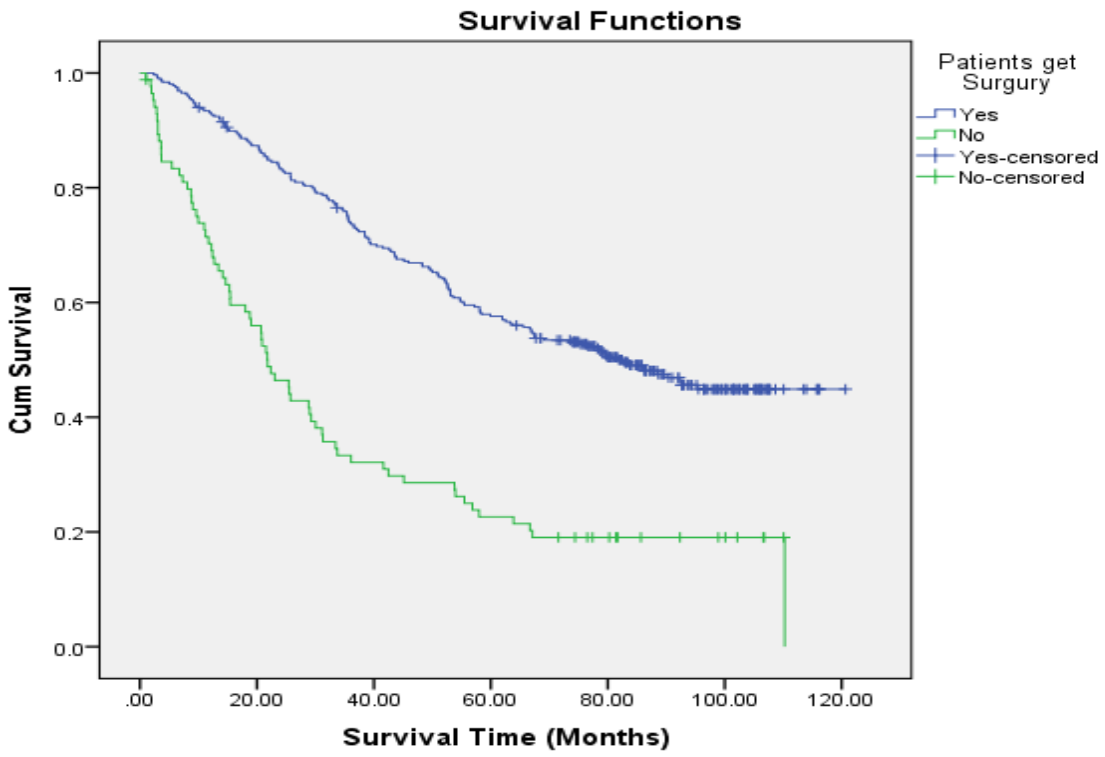

Figure 3. Overall survival rate of breast cancer patients who had got surgery as primary treatment at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, (N= 402), 2021.

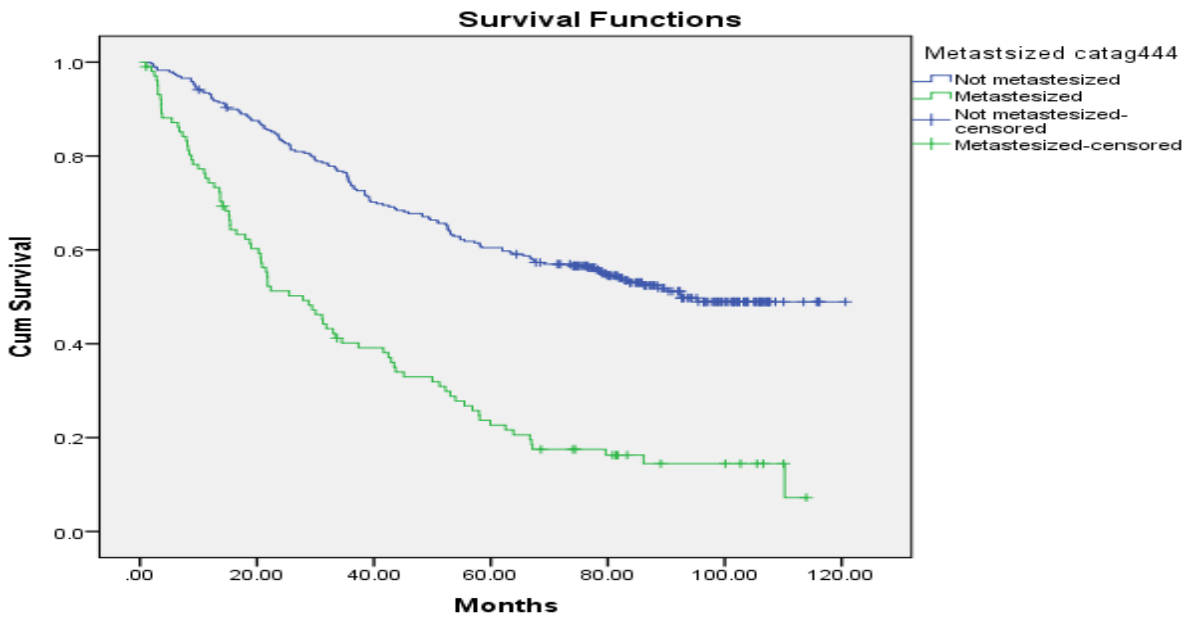

Figure 4. Metastasis status and overall survival rate of breast cancer patients treated at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, (N=402), 2021.

Table 4. Multivariable Cox regression for breast cancer patients attending treatment center at Tikur Anbesa Specialized Hospital (N=402), 2021.

			Univariate cox regration		Multivariate cox regration	
Factor	**N**	**Percent**	**HR† (95% CI)**	**P**	**HR∗(95%CI)**	**P value**
Stage at diagnosis						
I &II	84	21.6	1:00		1:00	
III	206	53.1	3.17 (1.97-5.08)	0.001	5.12(2.31- 11.36)	**0.001**
IV	98	25.3	7.65(4.68-12.51)	0.001	5.27(1.96- 14.18)	**0.001**
Nuclear grade						
Grade I	58	14.4	1:00		1:00	
Grade II	137	34.1	2.06(1.27-3.32)	0.003	2.33(1.03-5.26)	0.043
Grade III/ Undifferentiated	207	51.5	2.23(1.40-3.44)	0.001	1.82(0.814- 4.051)	0.145
Metastasis status						
No	290	74.0	1.00		1:00	
Yes	102	26.0	3.03(2.30-3.98)	0.001	2.01(1.13-3.56)	**0.018**
Surgery						
Yes	317	78.9			1:00	
No	85	21.1	2.85(2.15- 3.79)	0.001	1.38(0.81-2.35)	0.238
Hormone						
Yes	185	62.9			1:00	
No	109	37.1	1.48(1.08-2.02)	0.041	1.69(1.14-2.51)	0.010
Radiation						
Yes	128	48.1				
No	138	51.9	2.04(1.47-2.83)	**0.001**	1.47(0.943-2.29)	0.089

†Unadjusted Hazard Ratio; ∗Adjusted Hazard Ratio

Annex: VIII. Declaration

I the under signed, declared that this is my original work and has never been presented in this or any other any other university, and that all the sources and materials used for this dissertation , have been fully acknowledged.

Name: Fatuma Hassen (PI), (BA, BSc, MPH)

Signature: _____

Date: July 21/2023

Place: School of Public Health, Addis Ababa University

Date of examination: July 21/2023

This dissertation has been submitted for examination with my approval as University supervisor.

Name: Prof. Ahmed Ali

Signature: _____

Date: _____

Place: School of Public Health, Addis Ababa University

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Signature: _____

Date: _____

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