PATIENT AND DIAGNOSIS DELAYS AND SURVIVAL AMONG WOMEN WITH BREAST CANCER IN ADDIS ABABA, ETHIOPIA: A FOLLOW-UP STUDY

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Dedication

This dissertation is dedicated to all Ethiopian women who lost their lives and are currently suffering from the sequel of breast cancer due to lack of access to quality cancer care services.

List of original papers

This dissertation work is based on the following four original papers, which are listed hereunder.

I. **Gebremariam A,** Addissie A, Worku A, Assefa M, Kantelhardt EJ, Pace LE, et al. **Time intervals experienced between first symptom recognition and pathologic diagnosis of breast cancer in Addis Ababa, Ethiopia**. BMJ Open. 2019;9(11):e032228. DOI: 10.1136/ bmjopen-2019-032228

II. **Gebremariam A,** Addissie A, Worku A, Assefa M, Kantelhardt EJ, Jemal A. **Perspectives of patients, family members, and health care providers on late diagnosis of breast cancer in Ethiopia: A qualitative study**. PloS one. 2019;14(8):e0220769. DOI:10.1371/journal.pone.0220769.

III. **Gebremariam A,** Addissie A, Worku A, Assefa M, Pace LE, Kantelhardt EJ, et al. **Factors associated with late stage diagnosis of breast cancer among women in Addis Ababa, Ethiopia.** Breast Cancer Res Treat. 2021; 185(1): 117-24. DOI: https://doi.org/10.1007/s10549-020-05919-5.

IV. **Gebremariam A,** Addissie A, Worku A, Assefa M, Kantelhardt EJ, Jemal A. **Effect of delay in breast cancer diagnosis on survival of women with breast cancer in Addis Ababa, Ethiopia: A prospective cohort study** (Manuscript).

List of acronyms and abbreviations

AJCC	American Joint Committee on Cancer
aPR	Adjusted Prevalence Ratio
aHR	Adjusted Hazard Ratio
BC	Breast Cancer
BSE	Breast Self-Examination
CBE	Clinical Breast Examination
CI	Confidence Interval
DALYs	Disability Adjusted Life Years
IDIs	In-depth Interviews
IQR	Interquartile Range
LNR	Lymph Node Ratio
OR	Odds Ratio
OS	Overall Survival
PR	Prevalence Ratio
SD	Standard Deviation
TASH	Tikur Anbessa Specialized Hospital
TNM	Tumor Node Metastasis

Table of contents

Contents **Page number**

List of tables

Table number **Page number**

List of figures

Figure number **Page number**

Abstract

Background: Breast cancer is a leading cancer among women in Ethiopia. It accounts for one-third of all newly diagnosed female cancers. Most women with breast cancer in Ethiopia are diagnosed with late-stage disease, do not receive high-quality care, and face a poor prognosis. Locally relevant information on the extent of delayed diagnosis, reasons for late diagnosis, care, and determinants of survival among women with breast cancer is essential to guide clinical practices and public health policy. However, little is known about the extent and reasons for patient interval (from date of symptom recognition to the first consultation of health care providers), diagnosis interval (from consultation to diagnosis), and treatment initiation interval (from diagnosis to treatment initiation). Moreover, evidence on the relationship between patient delay (> 90 days)/diagnosis delay (> 30 days) and stage at diagnosis, and its effect on survival among women with breast cancer in Ethiopia is limited.

Objectives: To determine the magnitude of delays (patient and diagnosis delay) as well as stage at diagnosis and its effects on the survival of women with breast cancer in Addis Ababa.

Methods: The study employed mixed-methods (a cross-sectional study, a qualitative study, and a prospective cohort study). A cohort of 441 women newly diagnosed with breast cancer between 1st of January 2017 to 30th of June 2018 in Addis Ababa were recruited for the quantitative phase of the study, and followed prospectively for two years. Data were collected at different points in time, as a cross-sectional study (**Paper I and III**) and prospective cohort study design (**Paper IV**) to address the quantitative study objectives.

During recruitment, data on the participants' socio-demographic characteristics, date of first symptom recognition, and medical consultation after recognizing symptoms were collected using a structured interviewer-administered questionnaire. The date of diagnosis was taken from the patient's pathology report. One year after the recruitment, medical data, such as stage at diagnosis, date of diagnosis, histologic tumor type, date of receipt of treatment, and type were captured using a data extraction tool from the study participants' medical charts. Finally, at about two years following diagnosis, data related to survival status were obtained using both face-to-face interviews and telephone interviews. Also, medical charts were reviewed to update the treatment status of the study participants. We have conducted a univariable descriptive analysis to describe each variable. Multivariable Poisson regression with a robust variance model was used to determine the factors associated with patient/diagnosis delay and stage at diagnosis. Also,

Kaplan-Meier and multivariable Cox regressions were used to determine the overall survival rate and factors contributing to the overall survival of women with breast cancer, respectively. All statistical tests were assessed for significance at p-value < 0.05.

The qualitative study (**Paper II**) was conducted to explore the patients', family members', and health care providers' perspective on late diagnosis of breast cancer. It was employed among purposively selected 23 in-depth interviewees. Each of the audio recordings was transcribed verbatim, coded, and analyzed using thematic analysis.

Results: The magnitude of patient (>90 days) and diagnostic delays (>30 days) was 35.7%, 95% CI (31.1%, 40.3%) and 69.1%, 95% CI (64.6%, 73.3%), respectively. Patient delay was significantly higher among women who used traditional medicine before consultation (adjusted prevalence ratio [aPR] =2.13, 95% CI (1.68, 2.71). Diagnosis delay was significantly higher among women whose first consultation was at health centers (aPR=1.19, 95% CI [1.02, 1.39]) and those visited ≥ 4 facilities before confirmation (aPR=1.24, 95% CI [1.10, 1.40]) but lower among women who recognized progression of symptoms before consultation (aPR=0.73, 95% CI (0.60, 0.90).

The qualitative study revealed that pre-diagnostic awareness about breast cancer risk, causes, initial symptoms, early detection methods, and treatment was low. Disregarding the clinical importance of the first symptom or seeking care from traditional healers were noted as common practices among women with breast cancer that contributed to late diagnoses. Also, lack of awareness, and misperception about breast cancer treatment and its outcomes, competing priorities, financial insecurity, fear of diagnosis of cancer, and weak health systems (e.g., delay in referral and long waiting period for consultation) were identified as important causes of late diagnosis of women with breast cancer.

The median (interquartile range [IQR]) tumor size at diagnosis was 4 (3 to 6) centimeters. Sixty-four percent of the women (95% CI [59.5%, 68.8%]) were diagnosed at advanced-stages (44% stage III and 20% stage IV) of their disease. The prevalence of advanced-stage disease was significantly higher among women who used traditional medicine before diagnostic confirmation (aPR=1.29, 95% CI [1.10, 1.52]), and in those who waited for > 6 months before diagnosis (aPR=1.35, 95% CI [1.12, 1.63]). On the contrary, it was lower among women who had ever practiced breast self-examination before symptom recognition (aPR=0.77, 95% CI [0.63, 0.96]).

The median total interval (symptom recognition to first treatment initiation) was 7 (IQR: 2.7 to 15.7) months. One-fifth of the women started first treatment after one year of first symptom(s) recognition. Adjuvant chemotherapy initiation was delayed (>90 days) in 30% of patients. Only 31.4% (n=137) of the women had received radiotherapy, 64.2% (n=88) of which was adjuvant radiation. Adjuvant radiation initiation was delayed (>90 days) in 56.1% of the women.
The overall survival rate at year one was 88.3% (95% CI [84.9%, 91.0%]), and 75.2% (95% CI [70.7%, 79.0%]) at year two. Women diagnosed at stage I had a two-year survival of 100% in contrast to 26.7% at stage IV. The risk of death was significantly higher among women who had a symptom interval of >3 months (adjusted hazard ratio [aHR] = 1.87, 95% CI [1.15, 3.03]) and diagnosed with advanced-stages (aHR=3.32, 95% CI [1.81, 6.10]) but lower among those who had surgical (aHR=0.23, 95% CI [0.15, 0.35]) and hormonal therapy (aHR=0.26, 95% CI [0.17, 0.40]).

Conclusions: Substantial proportions of women with breast cancer in Addis Ababa have experienced patient and diagnostic delays that contribute to the high proportion of advanced-stage breast cancer, and low breast cancer survival rates. The factors identified that contribute to delayed diagnosis and advanced-stage diagnosis are modifiable. These include poor awareness about breast cancer, using traditional and spiritual remedies, downplaying the clinical importance of the first breast cancer symptoms, health care providers' limited provision of clinical breast examination and delayed referral of women for diagnosis with suggestive of breast cancer symptoms, and longer navigation process to get diagnosis. Once diagnosed, significant number of women experienced delay to adjuvant chemo-and radiotherapy initiation.

Recommendations: Breast health awareness campaigns that mitigate misconceptions and improve awareness about breast cancer both in the community and frontline health care providers are essential. Interventions to enhance early detection and prompt referral following consultation, and decrease waiting time between symptom recognition and breast cancer diagnosis are needed to improve early-stage diagnosis and survival rate of women with breast cancer. Also, the expansion of cancer diagnostic and treatment centers is necessary to shorten the diagnosis and treatment delays.

Keywords: Breast neoplasm, delay, time intervals, patient interval, diagnostic interval, symptom recognition, stage, survival, Addis Ababa, Ethiopia

1. Introduction

1.1. Background of the study

Cancer is one of the non-communicable diseases contributing to a significant number of deaths globally. In 2018, there were 18.1 million incident cancer cases and 9.6 million deaths worldwide [1], and cancer contributes to 213.2 million disability-adjusted life years (DALYs) [2]. The disease's burden is higher in developing countries where 56% of the incident cases, 62% of deaths, and 70% of DALYs occur [3]. The incidence of cancer and cancer-related death is increasing significantly in developing countries [2-3].

In Ethiopia, cancer is one of the common causes of disabilities and premature deaths [4], accounting for 3,192 age-standardized DALYs per 100,000. The burden of cancer [5-6], together with the other non-communicable diseases [7], is increasing in Ethiopia and other low and middle-income countries [2-3].

Among females, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths worldwide [1-2]. In 2018, breast cancer was the most commonly diagnosed cancer (24.2% of the 8.6 million new cancer cases) and the leading cause of cancer deaths (15.0% of the 4.2 million total cancer deaths) among women worldwide [1]. Estimates project that 5.8 million women will die from breast cancer by 2025 [8]. Though the incidence of breast cancer is not uniform throughout countries in Africa [9], it is on the top list of cancer in women in most countries while case fatality rate is higher in resource-limited countries [10-11].

In Ethiopia, 64,285 incident cancer cases were diagnosed in 2015, accounting for 33% of cancer in female and 23% of all cancer identified in Addis Ababa population-based cancer registry [12]. Breast cancer has significant public health and societal implications since it represents more than a third of all cancer cases in women, occurring frequently in young or middle age women [13-14] who are active in the workforce, raising children, and supporting other family members. The burden of breast cancer is rising [5-6] in part because of rapidly changing reproductive patterns [15], accompanied by increasing average age at first birth, decreasing fertility rate, and shifting dietary habits associated with rapid socioeconomic transitions.

1.2. Statement of the problem

Although breast cancer is the most prevalent cancer worldwide [1-2], its exact causes are still unknown, making identification of women at risk and primary prevention of the disease challenging [16]. However, a significant portion of the disease could be prevented by eliminating shared risk factors, mainly tobacco use, unhealthy diet, physical inactivity, and harmful use of alcohol [16], while encouraging early detection and initiation of appropriate early-stage treatments [17].

Early diagnosis and treatment is the main prevention strategy of premature death from breast cancer [17]. In Ethiopia, however, most women with breast cancer seek medical care at advanced-stages of the disease [13], which limits treatment options and decreases the chance of survival [18]. Two-thirds of women with breast cancer are diagnosed at the late-stage of the disease [13]. Furthermore, the choice of treatments is limited [4, 19] and tends to be located in university hospitals. These, together with the advanced-stage at diagnosis, are contributing to poor prognosis (i.e., 53% two years survival rate) [18].

In settings like Ethiopia with no national or regional breast cancer early detection program, early-stage diagnosis could be achieved by shortening the time intervals from symptom recognition to diagnosis of symptomatic breast cancer patients [20]. The reasons for late-stage diagnosis may include prolonged patient interval (time interval in seeking medical care after recognition of symptoms) and diagnostic interval (time intervals between initial medical consultation and diagnostic confirmation) [21-22]. These intervals have a significant effect on the stage at presentation [21-22] and treatment prognosis [20, 23]. However, the association between patient or diagnostic interval and stage at diagnosis is not consistently demonstrated across studies [20, 24-26]. Women who experienced patient delay (defined as > 3 months from the recognition of symptoms to the first consultation of health care providers) [27-28] had a 12% lower risk of survival compared to those who presented within 3 months [23]. Similarly, the diagnostic delay has been associated with lower survival [20]. Thus, understanding patients' pathways to diagnosis and the duration of these time intervals are essential to developing interventions to promote earlier detection.

Only three previous studies documented patient delay experienced by women with breast cancer in Ethiopia [14, 29-30]. Two of the studies were conducted ten years ago [29-30]. Dye et al. 2012

was a mixed-methods study based on 69 patients diagnosed between 2003 – 2007 in a referral hospital, Tikur Anbessa Specialized Hospital (TASH), which houses the only radiotherapy center in the country [29], while a third study was a retrospective study based on 404 patients treated from 1 October 2005 to 30 September 2015 in one private clinic [14], which means the findings may not reflect the current time interval patterns in Addis Ababa or nationwide. In this study, we investigated time intervals experienced by women with breast cancer, from the initial recognition of symptoms to the diagnosis of the disease. We also examined factors associated with patient and diagnostic intervals >90 days and >30 days, respectively. The findings from this study could inform public policy interventions aimed at shortening the time intervals, thereby potentiating a downstaging of the stage at diagnosis and improving survival.

Also, exploring the reasons for patient and diagnostic delays using a qualitative research method is essential to articulating an in-depth understanding of opinions, thoughts, and feelings of respondents and obtaining more contextualized information on the barriers encountered by the respondents [31]. According to Espina et al. [28], the reasons for the patient/diagnostic delays could be low educational attainment, lack of awareness on breast cancer and its detection methods, type of initial symptoms, fear of the disease or its treatment, traditional medicine use, financial difficulties, lack of access to healthcare, number and type of health care providers contacted before diagnosis, delayed referrals or non-referrals, misdiagnosis, wrong advice or false reassurances, and delays in obtaining diagnostic confirmation. This review was mainly based on quantitative studies, and may not have captured information that could be elucidated from qualitative studies through the probing of participants [31]. Also, the studies included were all based on data obtained before 2014, which situates the results in a time before various changes within Ethiopia and Africa, such as more political attention to cancer care [32], but late-stage disease presentation is still a major problem [33].

In Ethiopia, few qualitative studies used first-hand patient narratives to explore the specific barriers to early detection of breast cancer. Dye and colleagues, using mixed-methods, investigated the experiences of initial symptoms and actions [29], patient navigation [34] and beliefs and practices [35] of breast cancer in Ethiopia. These studies have documented that a substantial proportion of women with breast cancer first seek care in the form of traditional medicine, waited for about one and a half years before medical consultation, and face difficulties in navigating the healthcare system for timely diagnosis of their cancer. However, these results

were based on data collected approximately ten years ago and were limited to patients' beliefs and practices. Evidence from these studies may not reflect the current causes of late diagnosis of breast cancer in the country, given the rising burden of the disease and evolving healthcare system. Thus, understanding the current specific barriers to the early diagnosis that Ethiopian women with breast cancer are facing is vital for planning targeted interventions that help to mitigate premature death of women from breast cancer [36].

Also, to our knowledge, no previous study examined the factors associated with advanced-stage at diagnosis for breast cancer in Ethiopia. In this study, we examined the distribution and factors associated with advanced-stage at diagnosis among women newly diagnosed for breast cancer seen in seven major health facilities, capturing 90% of breast cancer cases recorded in the Addis Ababa population-based cancer registry.

Survival rate is the main prognostic indicator of breast cancer. Compared to developed countries, the survival rate is lower in resource-limited contexts like sub-Saharan Africa [37] mainly due to lack of early detection/screening strategy, late-stage detection, and limited treatment options [38-39]. In Ethiopia, few studies documented low survival rates of women with breast cancer [14, 18, 40]. Kantelhardt et al. [40] found 74% two-year metastatic free survival, while Eber-Schulz et al. [18] found a 53% two-year overall survival rate. Ersumo and colleagues also estimated 69.5% five-year overall survival among women with breast cancer attended a private medical center [14]. These studies found tumor size, receptor status, lymph node involvement, and age as the main predictors of survival [18, 40]. These studies were either based on retrospective chart review [14, 40] or prospective study [18] but lacked potential patient and health system-related predictors of the low survival rates.

Also, delays in seeking medical care after symptom recognition [23], and initiation of appropriate treatment [41-42] were associated with poor survival. Nonetheless, some literature found no effect of patient [20] or diagnostic [43] delay on the breast cancer patient survival. Despite the heterogeneous nature of the disease, the inconsistent relationship between delay and survival of women with breast cancer may reflect differences in methodological approaches across studies, such as lack of uniformity in the definition of delays, and cut points [44]. As most studies were retrospective makes them prone to data incompleteness and recall bias on matters such as dates of symptom recognition and first medical consultation. A prospective study assessing the effect of delay on the survival of women with breast cancer is essential to resolve this inconsistency. In

Ethiopia, however, we could not find a study assessing the relationship between patient or diagnosis delay and other characteristics predictive of survival of women with breast cancer. In this paper, we investigated the incidence of death among women with breast cancer, and the effect of diagnosis delay following symptom recognition on survival using a prospective cohort study. In addition, we have examined the treatment delays experienced by women with breast cancer in Addis Ababa.

1.3. Rationale of the study

Breast cancer is the leading cause of morbidity and mortality in Ethiopia [5-6]. The late-stage at diagnosis [13], along with the limited number of health facilities giving cancer care in Ethiopia [4, 19], contribute to poor prognosis. Unless these gaps are addressed, the mortality and morbidity burden from breast cancer will continue to increase in Ethiopia. The Federal Ministry of Health of Ethiopia has developed a National Cancer Control Plan drafted in 2015 aimed at improving early diagnosis of breast cancer through promoting early detection of symptomatic breast cancer patients and screening asymptomatic high-risk women by promoting breast self-awareness, and clinical breast examination for all women coming to health institutions for other conditions [45]. Generating local evidence about the magnitude of delayed diagnosis, the reasons for late diagnosis, and factors associated with advanced-stage at diagnosis of women with symptomatic breast cancer could help to achieve the goals of the national cancer control plan, downstaging, and improve the treatment outcomes of breast cancer.

As discussed in the above section, however, most of the studies conducted in Ethiopia were based on retrospective chart reviews, which may be affected by incompleteness and limited sample sizes thereby restricted their power to detect associations and inferences. Also, none of the studies examined the extent of delays contributed by the patients and diagnosis process, its causes, the relationship between patient/diagnosis delay and stage at diagnosis, as well as its effect on the survival of women with breast cancer in Ethiopia. There is also limited information on treatment patterns and delays, barriers to receipt of and completion of treatments, and patient-reported outcomes among women with breast cancer and other major cancers, which is crucial to guide public health policy and clinical practice.

In Ethiopia, the Addis Ababa cancer registry is the first national population-based cancer registry which was established in September 2011 at the Radiotherapy Center, TASH, and School of

Medicine of Addis Ababa University. The registry aimed to be the source of information on the burden of cancer in the city and for planning and monitoring cancer control activities in the country [5]. This registration is crucial for collecting accurate and complete cancer data that can be used for cancer control and epidemiological research, public health program planning, and monitoring patient care improvement [46]. The data collected by the registry format is, however, limited to selected variables (age, date of diagnosis, basis of diagnosis, site of the tumor, morphology, behavior, and stage of the tumor, treatment type received, date of last contact, and status of the last contact). Although information on the magnitude of patient and diagnosis delay, barriers to care, and the effects of the delays on the survival of the women with breast cancer are essential to guide clinical practices and public health policy, it cannot be captured from the cancer registry data. Thus, having a detailed investigation, such as the magnitude of patient and diagnosis delays, barriers to care, and determinants of survival, could help to enrich the information obtained from the cancer registrations. Therefore, we have conducted a prospective quantitative follow-up study mixed with qualitative methods to generate comprehensive information on the experiences of women with breast cancer from symptom recognition to survivorship. This study is the first prospective study on breast cancer patients' experience in Ethiopia intended to fill the existing information gaps concerning the magnitude of delays (patient, and diagnosis), factors associated with these delays and advanced-stage at diagnosis, and the effects of the delays on the survival of women with breast cancer. Also, we conducted a qualitative study to explore patient and health system-related reasons for late diagnosis of breast cancer from the patients', family members', and health care providers' perspectives in Addis Ababa. The findings of this study revealed and considered gaps and barriers to early diagnosis from different perspectives and provided fact-based material to develop "stories" that illustrate the compelling need for early-stage diagnosis of breast cancer.

In general, the findings of this dissertation can help health care providers, programmers, and policymakers to optimize the efficiency and quality of early detection and treatment of women with breast cancer. Also, it could encourage and help health care providers in Addis Ababa city and the country to improve their early detection practice via timely referrals of women with breast abnormalities, conducting clinical breast examinations as standard practice, and advising women to undertake regular breast self-examinations and seek immediate consultation after recognizing any breast abnormalities. Moreover, it may help in the formulation of local breast cancer care guidelines.

1.4. Literature review

1.4.1. Breast cancer types, origin and its classifications

Cancer is the result of an abnormal and uncontrolled proliferation of cells [47]. Cancer cells usually spread into the surrounding tissues or metastasize to distant organs through the lymphatic system or the blood [48]. Breast cancer is one of the common malignant tumors in humans arising from epithelial cells of glandular milk ducts or lobules of the breast. Breast cancer is a heterogeneous disease that can be classified into different subtypes considering its pathologic and molecular nature. Histologically breast cancer is categorized into in situ and invasive carcinoma. The invasive breast carcinoma can also be histologically categorized into different types, such as ductal, inflammatory, medullary, mucinous, medullary with lymphoid stroma papillary (predominantly micropapillary pattern), and lobular carcinoma [49]. Ductal carcinoma is the most common type of breast cancer. For instance, 59.0% of the women with breast cancer in Ethiopia had infiltrating ductal type breast carcinoma [50].

Also, breast cancer can be classified into different molecular sub-types considering estrogen, progesterone, and human epidermal growth factor 2 (HER2) statuses. According to these molecular factors, invasive breast cancer can be classified into luminal A (Estrogen and/or progesterone positive, and HER2 negative), luminal B (Estrogen and/or progesterone positive, and HER2 positive), HER2-enriched (Estrogen and/or progesterone negative, and HER2 positive), and triple-negative (Estrogen negative, progesterone negative and HER2 negative) breast cancer [51]. Majority of the breast cancer in Ethiopia are hormone receptor-positive [50].

1.4.2. Epidemiology of breast cancer

Breast cancer is the most common cancer among women globally [1, 3]. The incidence of breast cancer in men is rare, accounting for only 1% of breast cancer cases [3]. The rate of new cases and deaths from breast cancer is increasing having risen from 1.8 million new cases and 464,000 deaths [3] in 2013 to 2.08 million new cases and 626,679 deaths in 2018 [1]. Breast cancer accounts for 24.2% of all female cancer cases and 15.0% of all cancer deaths [1]. The incidence of breast cancer varies across the continents [1, 9]. The rate of increase and share of mortality of breast cancer is higher in developing countries [9].

The global age-adjusted incidence rate of new breast cancer cases and deaths estimated for 2018 was 46.3 cases/100,000 women and 13.0 deaths/100,000 women, respectively. The incidence rate

of new breast cancer cases ranges from 25.9 cases/100,000 women in South Africa to 94.2 cases/100,000 women in New Zealand [1]. The incidence of cases is higher in developed countries than the developing countries, but the death rate is vice versa [52]. The pooled crude incidence rate of breast cancer for Africa was 24.5 cases/100,000 person-years (95% CI [20.1, 28.9]) with varying incidence rates across the regions of Africa with the highest estimate for North Africa (29.3 cases/100,000) and a lower estimate for South Africa at 13.4 cases/100,000 [9]. This study revealed a notable increase in the incidence rates of breast cancer across the African regions over the last decades [9].

In Ethiopia, a cross-sectional study conducted in Tikur Anbessa Specialized Hospital in 2013 found breast cancer as the most prevalent type of cancer with 29.4% of cases followed by cervical cancer at 26.3% [53]. Of the estimated 64,285 new cancer cases seen in 2015, breast cancer accounted for 23% of all the cancers and 33% of the female cancers [12]. The estimated age-adjusted incidence rate of breast cancer among Ethiopian women ranged from 40.6 per 100,000 women [5] to 43.3 per 100,000 women [12]. The peak age interval at which the highest breast cancer frequency recorded was in the age range of 30 to 50 years [5-6].

In most cases, the exact causes of breast cancer are unknown. There are, however, established risk factors including genetic, environmental, and lifestyle factors. Mutation in identified breast cancer genes is one risk factor for developing breast cancer [54]. Hormones and growth factors also increase the risk of breast cancer. Older age at first birth is also considered a significant risk factor contributing to the increased incidence of breast cancer [55]. A Malaysian study found family history of breast cancer, history of benign breast disease, and use of oral contraceptive pills as statistically significant risk factors for breast cancer [56]. Different observational studies have also noted as the change in the lifestyle of the people is associated with an increased incidence of breast cancer [39, 54-55].

As a result, favorable lifestyle changes like increasing physical exercise or decreasing excess calories, alcohol intake, and obesity reduced the risk of breast cancer [39, 54-55]. Howell and colleagues noted that a favorable lifestyle could reduce up to 30% of the risk of breast cancer among all women [55]. This study revealed that about 50% of breast cancer among women at high and moderate risk of breast cancer could be prevented by using chemoprevention [55]. Higher parity [39], breastfeeding [39, 56], and eating a low-fat diet [56] were also identified as potential protective factors against breast cancer development.

1.4.3. Time intervals from symptom recognition to treatment initiation

Most breast cancer is sporadic and early detection and treatment is critical. In the absence of breast cancer screening program, women should immediately consult their physician once they recognize abnormality in their breast, and physicians should be suspicious and confirm the diagnosis as soon as possible. For various reasons, women with breast cancer seek medical care after their condition is advanced [38-39] at a higher likelihood in low-income countries than in high-income countries [57]. For example, a systemic review found a 30 to 48 day median interval between symptom discovery and treatment initiation in high-income countries, as opposed to between 3 to 8 months in low and middle-income countries [57].

The time interval from symptom recognition to treatment initiation of women with breast cancer can be seen as a component of intervals. However, the existing literature lacks consistency in the definition of the time intervals in women's journey with breast cancer [44]. The time intervals have been classified as "patient delay" and "system delay" [44, 58]. Some studies further refine these categories as patient delay, health care providers delay, referral delay, and diagnostic delay [59]. Literatures define patient delay as 12 weeks or greater from discovery of first breast cancer sign or symptom to initial presentation to any type of the health care facilities [27-28]. Whereas, health system or provider delay is defined as 2 weeks or greater from the first medical consultation to arrival to diagnosis center or diagnostic confirmation [58], and to initiation of treatment [60]. Harirchi and colleagues on the other hand considered diagnosis delay if the interval from first medical consultation and diagnosis exceeded one week [61]. Whereas, Norsa'adah and colleagues defined diagnosis delay if the interval from symptom recognition to histologic diagnosis exceeds 6 months [62]. For consistency, the Aarhus statement [63] recommended classifying these as "patient interval", "diagnostic interval", "treatment interval" and "total interval". Our study is based on this framework.

1.4.3.1. Patient interval

The patient interval was defined as the interval from the date of first recognition of symptoms (the time point when first bodily changes and or symptoms are noticed) to the date of first clinical presentation (the date at which the patient first presented to a health care provider after first recognition of symptoms) [63]. Within the literature, patient delay was defined as 12 weeks or

more from the recognition of the first breast cancer sign or symptom to initial presentation to any healthcare facilities [27-28] because it was associated with increased risk of death [23].

In Brazil Rio de Janeiro, the magnitude of patient delay among women with breast cancer diagnosed in 2015 was 34.3% [64]. Similarly, the magnitude of patient delay in China among those diagnosed from 2008 to 2012 was 40.4% [65]. The patient delay in developing countries is, however, significantly higher than in developed countries. For instance, the magnitude of patient delay in Rwanda was 85% [66]. Similarly, in Morocco, patient delay was recorded in 70.1% of women with breast cancer [67]. In Ethiopia, though studies assessing the time intervals are limited, on average, women were delayed for 18 months (between symptom recognition and treatment initiation) [29]. A more recent study based on a retrospective study found 73.3% of the women with breast cancer consulted for treatment after three months of symptom recognition [14].

Individual factors found significantly associated with increased patient delay included: being older [68], having lower socioeconomic status [64], traditional medicine use [58, 69], fear of treatment cost [27], and lower educational status [27, 58, 64]. For instance, a study conducted in Rwanda found that women with lower educational status had five times higher odds of patient delay compared to their counterparts [58]. A study conducted in Brazil also found a 60% higher odds of patient delay among women who had lower educational status (< 8^{th} grade) compared to those who had higher educational status (8^{th} or more) [64]. Similarly, patient delay was significantly higher among patients with no family history of breast cancer [64, 68]. But, patient delay was significantly lower among patients who knew breast cancer symptoms, practiced breast self-examination/clinical breast examination before symptom recognition [20, 68]. Patient delay was higher among rural residents compared to urban residents [70].

1.4.3.2. Diagnosis interval

The diagnostic interval was defined as the interval from the date of first clinical presentation to the date of diagnosis [63]. The date of pathologic diagnosis was the date at which histological or cytological examination results were documented. Diagnosis delay was defined as four weeks [69, 71] or more from the first medical consultation to date of diagnosis.

Not only the patient delay but also the delay experienced between consultation and diagnosis confirmation should be short. In China, only 15.5% of the patients experienced diagnosis delay

[65]. The diagnosis delay was higher among African Americans; 75% of whites received diagnosis within 2 months of symptom recognition compared to 60% of African Americans [72]. In Rwanda, 50% of the women diagnosed after 5 months of consultation [58] while 50% of the women in Morocco get diagnosed within 1 month of consultation [67].

The diagnosis delay experienced by the women may exceed the patient delay [73]. For example, a cross-sectional study from Thailand indicated that in a sample of 180 patients, 17% delayed seeking consultation for longer than three months, and 42% reported a diagnosis delay of longer than three months [73]. On the other hand, 82% of the women with breast cancer in Iran received the diagnosis of breast cancer within one week of their first consultation, and 72.7% of the patients received the first treatment within a week of diagnosis [61]. The scarcity of cancer diagnostic and treatment centers in Ethiopia is noted [19, 74], which leads to delayed diagnosis and treatment initiation of women with breast cancer in the country [29]. But, current evidence about the extent of diagnosis delay is lacking.

Though the cut-points varied across the literature, diagnosis delay was significantly higher among women having made ≥5 health facility visits before the diagnosis [58], practicing self-treatment, and longer travel time to the hospital, and increased number of surgical consultations before diagnosis [73]. Similarly, diagnosis delay was significantly higher among women who had self-detected first symptoms compared to those detected by screening [72]. Besides, diagnosis delay was more common among women who had wrongly reported their breast illness as non-malignant tumor during mammography or ultrasound examination [75]. This study also noted that long waiting time to get pathology results as contributing factor to diagnosis delay [75]. Diagnosis delay was observed among women who first visited public health facilities compared to those who visited private clinics [61].

1.4.3.3. Symptom interval

The patient and diagnosis intervals are mainly time-based classifications that may overlook the complex interaction between patient, societal, and health system factors that contribute together to both types of delay [76]. The patient and health system-related factors likely affect the stage at diagnosis and prognosis through the delay experienced between symptom recognition and diagnosis. This interval, as defined by the literature as symptom duration [21] or delay to diagnosis [77] or diagnosis delay [72], refers to the sum of the patient and diagnosis interval. In

our description, we used the naming ‘symptom interval’ to refer the time interval from the date of first symptom recognition to the date of pathologic report.

McKenzie and colleagues found that 71% of the women with breast cancer in sub-Saharan African countries get diagnosed after three months of symptom recognition, 33% get diagnosed after a year [21]. More than two-thirds (72.6%) of the women in Malaysia experienced a delay of three months and more before diagnosis confirmation [62]. A third of the women in New Jersey experienced delay of two or more months before diagnosis [72]. A study conducted in Rwanda indicated that the median symptom interval was 15 months; the median patient and diagnosis intervals were both five months [58].

The risk of having longer symptom interval (>3 months) among African American women (26.4%) was higher compared to white women (17.5%) [72]. Another study found longer symptom interval (> 6 months) significantly higher among women who used traditional medicines, false-negative diagnostic tests, misinterpretation of first symptoms, and lack of trust in conventional breast cancer treatment [62]. Women who used traditional medicine before diagnosis had about 3 times higher odds of longer symptom intervals (> 1 month) compared to their counterparts [69]. Risk of experiencing > 6 months delay before diagnosis was significantly higher among rural residents, among those who disregard breast cancer symptoms, used traditional medicines, and had fear of cancer diagnosis [67].

1.4.3.4. Treatment interval

Treatment interval was the time interval from the date of diagnosis to date of treatment initiation [63]. Once diagnosed, breast cancer patients should receive appropriate treatment as soon as possible [78]. There are different breast cancer treatment modalities: surgery, chemotherapy, targeted therapy, radiotherapy, endocrine therapy, and supportive therapy [79]. Various factors determine the choice of treatment types. The factors include the stage at diagnosis, risk of recurrence, receptor status, age, comorbidity [49, 79], availability of the choices, affordability by the patients, and their toxic effects [80].

Systemic therapy, which could be chemotherapy, endocrine therapy, and/or biological therapy for women with primary breast cancer, substantially decreases the risk of recurrence and increases overall survival [80]. However, the choice of breast cancer treatment in sub-Saharan African

countries is limited [19, 57] with the most typical treatments being surgery (70%), particularly mastectomy, followed by chemotherapy (60%), radiotherapy (46%), and endocrine treatment (38%) [39]. Mastectomy is not indicated for women diagnosed with metastatic cancer, but rather they require palliative therapy (chemotherapy and radiotherapy) and other supportive care. There must also be affordable opioids and trained personnel for palliative care [80].

A study conducted in Tikur Anbessa Specialized Hospital, Ethiopia, indicated that 87% of breast cancer clients received an operation, predominately modified radical mastectomy (95%). The majority of patients (83%) also received chemotherapy (primarily anthracycline-containing chemotherapy) [40]. Despite its curative and palliative advantage of radiotherapy, in Ethiopia, we have only one radiotherapy center. Only a quarter of the patients (26.6%) in demand for radiotherapy received radiation therapy [81], and the majority of the radiotherapies were given for palliative therapy [82].

Timely initiation of appropriate treatment improves the prognosis of women with breast cancer [78]. Thus, not only the health-seeking and diagnosis delay but also the treatment initiation delay (delay experienced between diagnosis and initiation of treatment) [41-42, 83] affect the survival of women with breast cancer. McLaughlin et al. [41] documented an 85% higher hazard of death for women with breast cancer who delayed initiation of treatment 60 days or higher [41]. Similarly, Smith et al. [83] revealed 82% higher hazard of breast cancer caused death among the women who had started treatment after six weeks of their diagnosis compared to those who began within two weeks of diagnosis. One of the treatment modalities is chemotherapy, and literature recommends initiation of adjuvant chemotherapy within four [18, 37, 78] to twelve weeks of surgery [84]. In a ten-year follow-up study, Heeg et al. found a 69% increased risk of death among women who initiated adjuvant chemotherapy after four weeks of surgery compared to those who received it within four weeks [85].

In the USA, only 21.8% of the breast cancer patients experienced delay of treatment initiation (defined > 2 months) [86]. In contrast, more than half of the breast cancer patients in Botswana experienced treatment initiation delay of > 3 months [87].

Determining the delay to the receipt of the appropriate therapy and its causes is essential to design interventions targeted at shortening the waiting times and improving breast cancer survivors' survival. In Ethiopia, studies assessing delay in initiating treatment modalities after

breast cancer diagnosis are lacking. Feuchtner et al. [81] and Rick et al. [82] investigated the pattern of therapy for the common cancers (breast cancer was one of them). Feuchtner et al. [81] found 2.1 months median waiting time between surgery and adjuvant chemotherapy initiation. Rick et al. [82] found longer waiting for the patients who received adjuvant radiation therapy (median, 150 days; Interquartile range [IQR]: 60 to 210 days) than those who received palliative radiotherapy (median, 0 days; IQR: 0 to 15 days). However, these two studies were based on retrospective chart reviews and were not specific to breast cancer.

1.4.4. Causes of delayed diagnosis of breast cancer

The causes of the delays are multifaceted [29, 58, 76]. The classification of the delays is mainly time-based classification. In contrast, the underlining causes of patient, diagnostic, or treatment initiation delays are not mutually exclusive but complex interactions between patient, societal, and health system factors [76]. We have, however, summarized some of the causes for the delays as follows.

The common method of breast cancer detection methods, especially in resource-limited countries, is breast self-examination (BSE) and clinical breast examination (CBE) [39]. However, women's knowledge of these early detection methods, risk factors, first symptoms, and breast cancer treatment is low [88-89]. For instance, a study conducted at Mekelle University found the knowledge on risk factors, early screening measures, and clinical signs of breast cancer among female students was 1.4%, 3.6%, and 22.1.%, respectively [88]. Another study conducted in Addis Ababa revealed that 47% of the participants have never heard of breast cancer; only 35.5% of the participants knew at least one type of early detection method. The magnitude of ever practice of BSE, CBE, and mammographic examination was 154 (68%), 48(21%), and 24 (11%), respectively [89]. Lack of knowledge of breast cancer was worse among older women [90]. Not only women but also female health care providers were found to have low levels of experience on breast cancer [91]. Lack of knowledge of the screening methods and first breast cancer symptoms was associated with patient delay [60]. Moreover, the lack of knowledge on where to go after recognition of the first symptoms contributed to the delayed diagnosis and treatment initiation of women with breast cancer [29].

Many women failed to initially recognize a breast lump, which is the most frequent first symptom of breast cancer [61], as clinically relevant [27] and even think of the lump as self-limiting [38,

58] or as benign symptoms, such as cyst, slime, knot or a sign of menses [92]. Types and severity of the first symptoms: the presence of breast ulcer, lack of pain, and the presence of palpable axillary lymph nodes were moderately linked to patient delays [60].

Some women misperceive the cause of cancer; they tend to link the cause to sunstroke locally termed as “mitch” (an Ethiopian ethnomedical category roughly equivalent to 'bad air'), and breastfeeding problems [35]. As a result, many women in Ethiopia [35, 93] and elsewhere [94] tend to use different alternative medicines before consulting medical care. Dye and his colleagues in Addis Ababa revealed that 16.4% of the women at their first sign of breast cancer visit traditional healers (16.4%) [34]. Some women seek medical care after recognizing that their disease is getting worse or advanced [74, 80].

Contrary to lack of knowledge, fear of cancer diagnosis and its treatments [60], fear of partner abandonment, embarrassment disclosing symptoms to health care professionals, taboo, and fear of stigma [95] were also noted as the causes of delayed consultation. Many people consider breast cancer as a non-treatable or fatal disease [74].

Healthcare-related factors also contribute to the delayed consultation, diagnosis, and treatment initiation of breast cancer [38, 57, 60]. Access to healthcare and the quality of the available healthcare service contribute to the delayed care of women with breast cancer [38, 57, 74]. Access to care, cost of biopsies, pathology, and treatment modalities like chemotherapy are the barriers to care [74].

Health professionals should be the primary source of information and role model to the public on breast cancer. However, different pocket studies indicated that breast cancer knowledge, especially among frontline health care providers is low [91, 96]. A study conducted in Addis Ababa, Ethiopia, among female nurses indicated that only 57.8% were knowledgeable on breast cancer [91]. Another survey conducted among health extension workers (HEWs) revealed low knowledge and practice of breast cancer screening: only 30.4% mentioned at least one screening method for breast cancer, and 37.3% practiced BSE during their lifetime [96]. As a result, health care providers' role in information dissemination about breast cancer to the women was minimal [97]. Thus, health care providers also contribute to the women's delay to medical care-seeking and breast cancer diagnosis. Due to low knowledge of breast cancer symptoms and signs, health care providers may fail to suspect and refer the women with early symptoms of breast cancer for

diagnostic confirmation [28]. Presentation with other than lump, providers misdiagnosis' and inadequate patient examination, use of inappropriate tests or failing to follow-up negative or inconclusive test results, false-negative diagnostic tests, and non-cancer interpretation were predictive risk factors for the diagnosis delays contributed by the health care providers [28].

Context-specific information and understanding of the patients' pathway to diagnosis and the delays experienced are essential to design interventions targeted at enhancing early stage diagnosis and treatment of breast cancer. In Ethiopia, however, there is minimal evidence with only three studies examining patient delay among breast cancer patients using patients seen at Tikur Anbessa Specialized Hospital (TASH) [29-30] and one private clinic [14]. Using a mixed study design, Dye and colleagues have investigated the experiences of initial symptoms and actions [29-30] of breast cancer in Ethiopia. These studies have documented that a substantial proportion of women with breast cancer first seek care in the form of traditional medicine, waited for about one and a half years before medical consultation, and face difficulties in navigating the healthcare system for timely diagnosis of their cancer. However, these results were based on ten-year-old data from a relatively small (69) sample of breast cancer patients from a single specialized hospital. These studies were also limited to the beliefs and practices of patients.

1.4.5. Stage at diagnosis of breast cancer

The stage at diagnosis determines the type of treatment and patients' prognosis after treatment, as well as to report the treatment outcomes uniformly [49, 98-99]. The most commonly used staging system is the tumor node and metastasis (TNM) designed by the American Joint Committee on Cancer (AJCC). According to the 7th edition of the AJCC, Breast Cancer Staging Manual, during the staging of breast cancer, the size and extent of the primary tumor, involvement of the regional lymph node, and the presence or absence of distant metastases are considered [49].

In addition to the TNM, tumor biology, such as grade, hormonal receptor status, and human epidermal growth factor receptor 2 are essential determinants of prognosis and incorporated in the staging of breast cancer [99]. Nonetheless, laboratory centers that determine tumor biology are scarce, especially in developing countries like our country. Thus, the staging is undertaking using the TNM staging [49]. The TNM staging could be clinical (cTNM), pathological (pTNM), and post-therapy stage (yTNM), and classified into stage I, II, III, and IV [49]. Usually, stage I and II are considered as early stage, while stage III and IV as advanced-stage disease [10, 26].

The stage at diagnosis is the most determinant factor of the survival of women with breast cancer. The survival rate of women diagnosed with stage I breast cancer is much higher than those diagnosed with stage IV [98]. However, most of the women with breast cancer in sub-Saharan Africa are diagnosed at an advanced-stage. The proportion of advanced-stage at diagnosis among sub-Saharan African countries (64.9%) [10] is much higher than the developed countries like the United States of America (26.6%) [100]. This proportion is, however, not uniform across the sub-Saharan African countries [26]: it ranges from 30.3% to 100%. In Rwanda, 76% of the women were diagnosed with advanced-stage [58]. In Ethiopia, according to the few pieces of evidence available, most women are diagnosed at an advanced-stage [14, 33, 40]. For instance, Deressa and colleagues [33] found that 85% of the women in the rural part of Ethiopia were diagnosed at an advanced-stage of breast cancer. Kantelhardt et al. [40], based on record review, also found 36% of the women with breast cancer diagnosed at stage III.

The cause of the late-stage diagnosis could be complex, but, it could be primarily due to patient or diagnostic delay [32, 58, 63, 101]. The delay between symptom recognition and initiation of treatment is mere weeks in developed countries [57] while months and even years in developing countries [58]. For instance, Unger-Aldaña et al. [57] found women in developed countries waited for only 30-48 days between notification and treatment, and >70% of the women diagnosed at an early stage. On the contrary, women in developing countries waited for 3 to 8 months between notification and treatment, and only 20-50% were diagnosed at an early stage. A study in Rwanda [58] documented fifteen-month delays from symptom recognition to diagnosis, and less than one-fourth of the women diagnosed at an early stage (stages I and II).

The effect of patient or diagnosis delay, however, was not consistently demonstrated across the previous literature. Love et al., and Ángeles-Llerenas et al. found patient delay contributed to the advanced clinical stage [20, 24]. On the contrary, Redondo et al. [25] revealed that shorter patient delay (< 30 days) is associated with advanced-stage at diagnosis. Williams and colleagues [102] also found that shorter diagnostic delay is related to a higher risk of advanced-stage at diagnosis. In contrast, Jedy-Agba et al. [26] found no association between symptom interval (interval from first symptom recognition to diagnosis) and advanced-stage at diagnosis.

This inconsistent association could be partly due to the variation of the definition of the time intervals used across the studies, data incompleteness, and residual confounders because the studies were mainly record review. Addressing the inconsistent relationship between

patient/diagnosis delay and advanced-stage at diagnosis, as well as identifying modifiable causes of the advanced stage at diagnosis in Ethiopia, is essential to downstage the late-stage diagnosis. Also, to our knowledge, no previous study examined the factors associated with advanced-stage at diagnosis for breast cancer in Ethiopia.

Other factors associated with advanced-stage at diagnosis included age at diagnosis [73], education status of the women [73, 103], family income, travel time to referral hospital and the number of consultations with a surgeon [73], having low socioeconomic status [103], and health facilities distance from home [104]. The association between age and stage at diagnosis, however, is not consistent across the evidence. Mohaghegh et al. [103] found no significant difference in the stage at diagnosis with the age of the women, and Yeo et al. [90] revealed a higher advanced-stage among young women compared to older women. According to this study, higher proportion of grade 3 tumor, lymphovascular invasion and presence of multifocal disease was observed among young women with breast cancer compared to their older counterparts [90].

1.4.6. Survival rate among women with breast cancer

The global pooled overall survival rates of women with breast cancer at 1-, 3-, 5-, and 10-year was 92.0%, 75%, 73.0%, and 61%, respectively [105]. The survival rate of women with breast cancer in developing countries is much lower than the developed countries [105]. For instance, the pooled 5-year overall survival for African region was about threefold lower than for the Western region [105]. Joko-Fru and colleagues [10] estimated the overall survival rate at 1-, 3-, and 5-year for sub-Saharan African countries was 84.1%, 61.4%, and 52.3%, respectively. A significant increase in survival rates has been observed during the last decades; however, the improvement in resource-limited countries is minimal compared to those of developed countries [105]. Survival rates of women with breast cancer across the sub-Saharan African countries also vary according to national human development indexes [10].

In Ethiopia, few studies estimated the survival rate of breast cancer [13, 18, 40], which is far lower than the estimates for global and sub-Saharan African countries. Kantelhardt et al. [40] found 74% and 46% metastatic free survival at 2- and 5-year, respectively. The incidence of distant metastasis within a five-year follow-up time was 26.6%. Weiner et al. also estimated the median overall survival for women with metastatic breast cancer, reporting a finding of 6.6

months (range from 0 to 138 months) [13]. Eber-Schulz et al. [18] estimated 1- and 2-year overall survival rates for rural women with breast cancer at 78% and 53%, respectively.

The discrepancy in the survival rate across different countries and individuals could be explained by the various individual, healthcare, and country-level factors. Stage at diagnosis is the main predictor of survival of women with breast cancer [10, 13, 105]. According to Maajani et al.'s [105] estimation, the global 10-year pooled overall survival for women with stage I was threefold higher than for those with stage IV. About two-thirds of the breast cancer cases in developing countries are diagnosed at an advanced-stage [10], contributing to the lower survival rate [105] contrary to the developed countries where only 26.6% were diagnosed in an advanced-stage [100].

The literature revealed that patient delay is positively related to advanced-stage at diagnosis of breast cancer [106], and advanced-stage at diagnosis is a significant negative predictor of the survival of women with breast cancer [10, 13, 20, 105]. The patient delay has a direct negative impact on the treatment prognosis and survival of women with breast cancer. Women who presented beyond 3 months had a 12% lower 5-year survival than those with shorter delays, and those with delays of three to six months had 7% lower survival than those with shorter delays [23]. Nonetheless, the independent effect of patient delay (after adjusting for the stage at diagnosis) is inconclusive across the literature. The four articles included in this review do not have enough evidence to reject the null hypothesis, no difference [20, 24-25, 107]. A Mexican study also documented the absence of a statistically significant relationship between total delay (from first symptom recognition to the initiation of treatment) and survival [20]. However, these inconclusive findings may have been due to factors not accounted for in these studies. First, the sample size used to calculate the excess risk of death in those with patient delay might be of inadequate power to detect a significant difference. Second, those patients who sought medical care immediately after recognizing the symptoms may be those with more aggressive forms of the disease [25]. Previous studies also documented not only a nonsignificant relationship between patient delay and survival but also a protective relationship [108]. Tjemsland et al. [107] justified as rapid progression of symptoms or signs can lead the patient as well as the doctor to react quickly, which finally might lead to death in a shorter time interval than those with slow progressing tumors. Third, the cut-off point used to define the patient delay lacks uniformity

across the reviewed articles [20, 24-25, 107]. Lastly, patient delay is subjected to recall and social desirability bias.

After diagnosis, most studies suggest that women should receive appropriate treatment as soon as possible since delayed treatment initiation impacts the survival of women with breast cancer [41, 83, 109-110]. Nonetheless, the relationship between the late initiation of the first treatment and survival has not been consistently demonstrated. Some studies have found a nonsignificant relationship between delay in treatment initiation and survival of breast cancer [20, 43, 111-115]. During our review, there was methodological variation between the studies that potentially nullifies the effect of treatment initiation delay and those which detect a significant impact. For example, the sample size of the articles which nullify the effect of delay in treatment initiation [20, 43, 111-115] was relatively smaller, ranging from 301 to 1702 breast cancer cases compared to those articles which found a significant effect of delay on the survival of women with breast cancer [41, 83, 109-110], which ranged from 1786 to 115,790 cases. Thus, the sample size might have impacted the power of the study to detect statistically significant differences. In addition to the sample size, the four articles which found a significant association between treatment delay and survival were population-based studies [41, 83, 109-110].

In contrast, these articles that found nonsignificant associations were based on women attending one or more hospitals [20, 43, 111-115]. Lastly, researchers recommended computing breast cancer-specific survival instead of overall survival because overall survival can be diluted by non-breast cancer-specific deaths [116]. Most of the reviewed articles that found no association between treatment delay and survival have computed overall survival [43, 112-115]. In contrast, the articles which declared a negative effect of treatment delay on survival [41, 83, 109-110] have computed breast cancer-specific survival.

Cut-off points used to define treatment delay varied across the studies. For instance, Angeles-Llerans et al. [20] used interquartile range and categorized the variable into four segments, Smith et al. [111] treated it as a continuous variable, Yoo et al. [43] dichotomized as 0-29 days versus $\geq$30 days, and others as <90 days versus $\geq$90 days [113-114]. This variation could have contributed to the inconsistent findings on the relationship between treatment delay and breast cancer patients' survival [117].

Other factors associated with the survival of women with breast cancer included having comorbidities [118], the tumor's molecular subtype [119-120], histology [40], and grade [121-122]. Women with receptor-positive breast cancer have a lower risk of recurrence, and a higher survival rate than their counterparts. Patients with ductal histology [40] and lower tumor grades [121-122] were found to have better survival rates compared to their counterparts. Women with Grade 2 tumors had about twice higher risk of death compared to those with Grade 1 tumors [121].

Women with breast cancer need a continuum of care. Every woman with breast cancer should have a regular follow-up with attention paid to recurrence and long-term side effects, such as osteoporosis [123]. The post-treatment quality of life of women with breast cancer is a good predictor of their overall survival. Psychosocial support should be part of the continuum of care because it also has a significant effect on the patients' survival rate [124].

In summary, breast cancer is the most common cancer among women worldwide with an increased burden of morbidity and mortality in developing countries. Early detection and treatment initiation are essential to reduce mortality. However, the majority of women in Ethiopia and other developing countries seek medical care when their disease is already at an advanced-stage. The cause of the late-stage diagnosis is multifaceted, which could be encapsulated by patient and diagnosis delay. The association between patient or diagnosis delay and advanced-stage at diagnosis is not consistently demonstrated across studies. Also, the association between the delays and survival of the women with breast cancer is, inconsistent across the literature.

1.5. Conceptual framework

The conceptual framework is built after reviewing different literature and mainly adapted from Weller et al. [63] and Unger-Saldana et al. [76] (Figure 1). The conceptual framework comprises various factors which influence one another in the journey of women with breast cancer from recognizing symptoms to diagnosis, receipt of treatment, and survivorship care. It shows the interrelationship among patient interval, diagnosis interval, stage at diagnosis, and prognosis after treatment.

The causes of patient and diagnosis delay are interrelated. According to the review, the patient delay is related to the lack of knowledge, and misconceptions about breast cancer, the practice of breast cancer screening methods like BSE, CBE, and mammography examination, appraisal of the first symptoms and signs of breast cancer, downplaying the importance of first symptom(s) of breast cancer, perceived risk of susceptibility to breast cancer, fear of cancer diagnosis and treatment, fear of discloser, lack of knowing where to go after recognition of first symptom(s) of breast cancer, perceived causes of breast cancer, and using traditional medicines like herbals and holy water. Besides, it is also related to individual factors like older age, lower educational and socioeconomic status, time constraints, and family history of breast cancer, as well as access to healthcare. Diagnosis delay is related to access and quality of the service, cost of care, misdiagnosis, and waiting time for laboratory results. Patient and diagnosis delay is associated with advanced-stage at diagnosis, and stage at diagnosis, together with other tumor characteristics, affects the choices of therapy, and probability of survival.

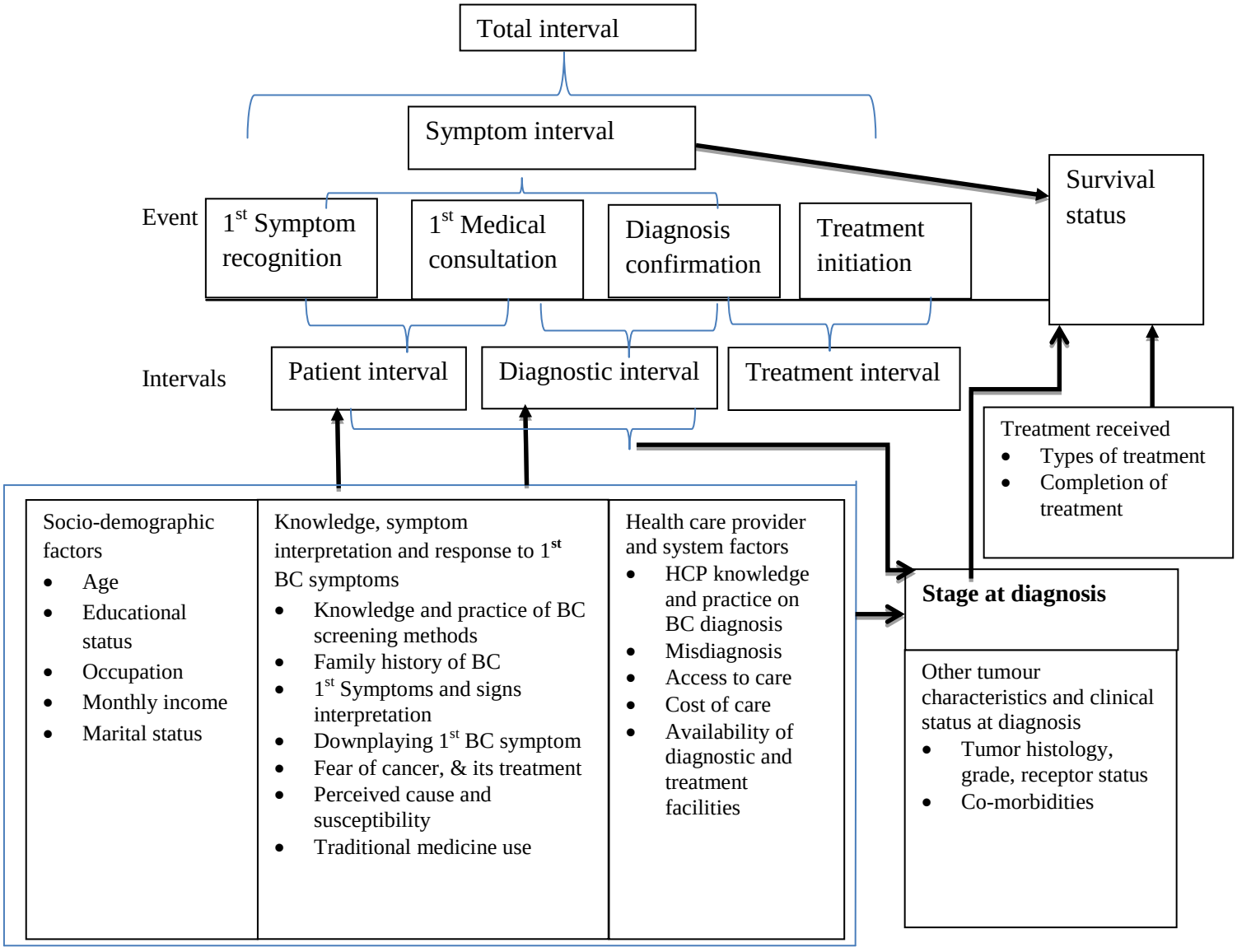

Figure 1: Conceptual framework for patient and diagnosis delays and survival among women with breast cancer (adapted from Weller et al. [63] and Unger-Saldana et al. [76])

2. Research questions and objectives

2.1. Research questions

- How long do women with breast cancer in Addis Ababa elapse to seek medical care and diagnosis?
- What factors are associated with patient and diagnosis delay among women with breast cancer in Addis Ababa city, Ethiopia?
- Why are women with breast cancer in Addis Ababa city, Ethiopia diagnosed late?
- What are the factors associated with advanced-stage at diagnosis of women with breast cancer in Addis Ababa city, Ethiopia?
- What is the two-year overall survival rate of women with breast cancer in Addis Ababa city, Ethiopia?
- Is there an association between delay, stage at diagnosis, and overall survival of women with breast cancer in Addis Ababa city, Ethiopia?

2.2. General objective

- To determine the magnitude of delays (patient and diagnosis delay) as well as stage at diagnosis and its effects on the survival of women with breast cancer in Addis Ababa city

2.3. Specific objectives

1. To determine the magnitude of delays (patient and diagnostic), and factors associated with these delays of women with breast cancer in Addis Ababa city (**Paper-I**)
2. To explore the reasons for late diagnosis of women with breast cancer in Addis Ababa city (**Paper-II**)
3. To identify factors associated with advanced-stage at diagnosis of women with breast cancer in Addis Ababa city (**Paper-III**)
4. To determine two-year survival rate and its associations with delay and stage at diagnosis of women with breast cancer in Addis Ababa city (**Paper-IV**)

2.4. Research hypotheses

1. Delay (patient and diagnosis) is associated with increased risk of advanced stage at diagnosis of women with breast cancer in Addis Ababa city, Ethiopia.
2. Delay (patient and diagnosis) is associated with increased risk of death of women with breast cancer in Addis Ababa city, Ethiopia.

3. Methods

3.1. Study area and period

This dissertation is part of a large project entitled “Breast and Cervical Cancer Patients' Experience in Addis Ababa City, Ethiopia: A follow-up study” [125]. The study was conducted in Addis Ababa, the capital city of Ethiopia with an estimated population of 3.5 million [126]. According to the city government of Addis Ababa Bureau of Finance and Economic Development 2013/14 report, the city has ten sub-cities and 116 districts.

There are 11 public and 33 private hospitals in the city, 88 public and 6 non-governmental health centers, and 777 private clinics [127]. According to a national survey, the leading health care providers for outpatients were government health facilities (77%), followed by private health facilities (20%), traditional and religious healers (2%), and non-governmental organizations (1%) [128].

The Ethiopian health service is structured into a three-tier health system: primary, secondary, and tertiary healthcare levels connected by a referral system. The primary health care service points for urban settings like Addis Ababa include health centers, private clinics, and primary hospitals, while secondary and tertiary healthcare levels are composed of general hospitals and specialized hospitals, respectively. Compared to hospitals, health centers are more likely to be staffed by nurses and health officers (graduate of a four-year training program in biomedical, clinical, and public health courses), and mainly provide preventive and primary care [129]. Specific to breast cancer, health center staff are expected to create community awareness on the availability and importance of clinical breast examination services and refer women suspected of breast cancer to general hospitals for diagnostic services [45].

In Addis Ababa, a population-based cancer registry has been in place since 2011, with incident cases collected from 17 health facilities, including referral hospitals, higher clinics, and diagnostic centers [5]. The main sources for the registry in Addis Ababa city are hospitals (Departments of Pathology, Hematology, Pediatrics, Gynecology, Surgery, and Internal Medicine), radiotherapy centers, higher diagnostic clinics, and diagnostic laboratory with pathology services. This project recruited all women with breast and cervical cancer aged $\geq$18 years diagnosed from January 1, 2017 – June 30, 2018 in 7 major health facilities. Of which, two are public (TASH, and St. Paul Hospital Millennium Medical College) and five are private

(United Vision Medical Services Center, Hallelujah General Hospital, Betezata Hospital, Legehar Hospital and Landmark Hospital). These health facilities capture more than 90% of all women with breast and cervical cancer reported to the cancer registry in Addis Ababa. In addition to the above seven recruiting health facilities, the monthly report of the Addis Ababa cancer registry cancer notification form was assessed to identify eligible women who were not captured in the seven health facilities. These women were contacted by phone for their place of follow-up and convenient date and time to meet for interviews. Recruitment of the study participants has been started on March 20, 2017, and ended at June 30, 2018. The project 441 women newly diagnosed for breast cancer over the 18 months recuitement period. This project was conducted to address nine specific objectives [125].

However, to focus and limit the size of the dissertation was mainly based on the five of the nine specific objectives of the larger project. The quantitative study (**Paper I, III and IV**) was conducted in seven major health facilities. Also, the monthly report of the Addis Ababa cancer registry cancer notification form was assessed to identify eligible women who were not captured in the seven health facilities

While the qualitative study (**Paper II**) was conducted at Tikur Anbessa Specialized Hospital (TASH) Oncology Center. Tikur Anbessa Specialized Hospital is a teaching hospital of the College of Health Sciences of Addis Ababa University and a tertiary referral hospital for the country. The hospital has a separate building for cancer treatment (oncology clinic) which serves as a referral hospital for cancer care and hosts the only radiotherapy machine in the country. The study was conducted from March to July 2017.

3.2. Study designs

Mixed research with convergent parallel study design was employed [130]. A convergent parallel mixed method is a type of design in which qualitative and quantitative data are collected in parallel, analyzed separately, and then merged during interpretations. In this study, the quantitative follow-up study was conducted to determine the magnitude of the delays, advanced-stage at diagnosis, the effect of delayed diagnosis following symptom recognition and stage at diagnosis on the survival of women with breast cancer, while the qualitative study was conducted to explore the reasons for late diagnosis from patients', family members', and health care providers' perspectives. The qualitative study was conducted to complement the survey results

and provided an in-depth understanding [131] of the reasons for late diagnosis of breast cancer from different perspectives.

Paper-I and III addressed a cross-sectional study design component of the study, while **paper IV** addressed a prospective cohort study design element. **Paper II** reflected the qualitative study component which addressed using a phenomenological study since this method is useful in studying participants' lived experiences of a phenomenon [132]. In this case, it captured the experience of breast cancer diagnosis and reasons for late diagnosis from patients', family members', and health care providers' perspectives (Figure 2).

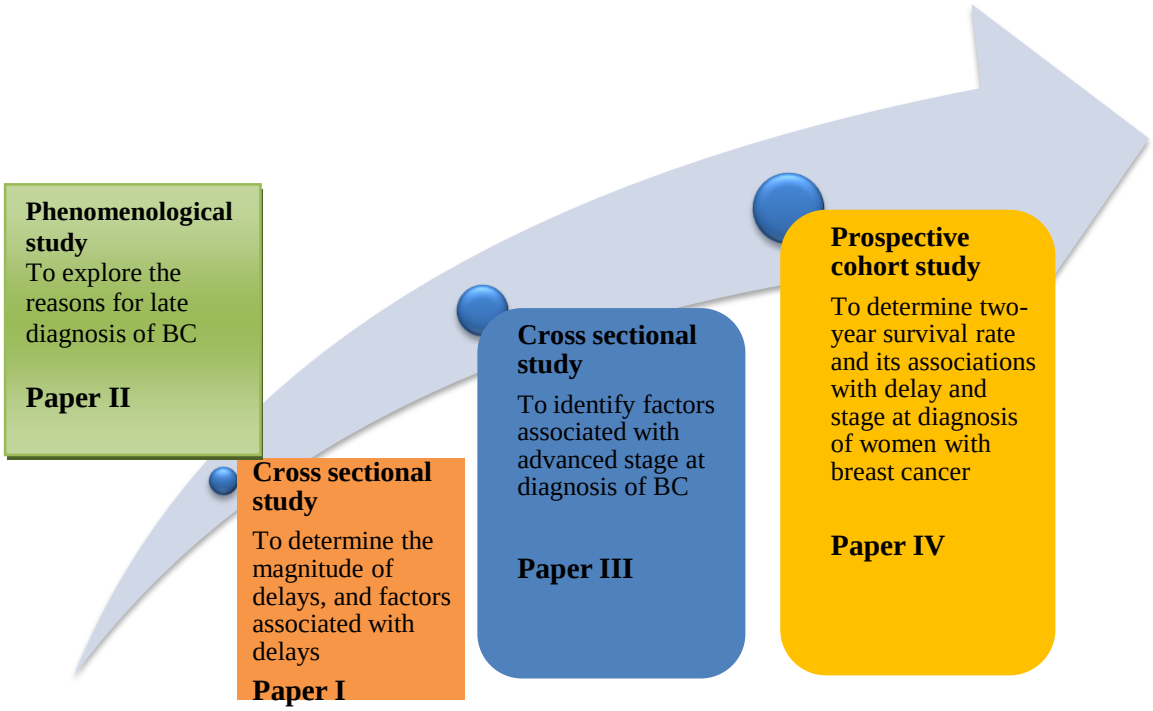

Figure 2: Summary of the study objectives and designs of the dissertation, Addis Ababa, Ethiopia

3.3. Source and study population

For **papers I, III and IV**, the source population were all women with breast cancer aged 18 years and above from Addis Ababa city. The study population was all women aged >18 years with newly diagnosed breast cancer between 1 January 2017 and 30 June 2018 from Addis Ababa city.

For **paper II**, women with breast cancer, family members and health care providers were involved in the study. The study populations were: 1) Women aged 18 years and above who were diagnosed with breast cancer in 2016; 2) Family members aged 18 years and above whom accompanied women with breast cancer diagnosed in 2016 and 3) Health care providers who have been providing care to cancer patients at the oncology clinic.

3.3.1. Inclusion and exclusion criteria

For **papers I, III, and IV**, eligible study participants were residents of Addis Ababa City at the time of diagnosis, with incident breast cancer diagnosed between 1 January 2017 and 30 June 2018. Recurrent breast cancer or those with prior history of any other cancer were excluded from the study.

For **paper II**, the women had to meet the inclusion criteria being aged 18 years and above, diagnosed with primary breast cancer in 2016 and attended at the oncology clinic, capable of making the interview and residents in Addis Ababa city for more than 6 months before diagnosis. Similarly, family members aged 18 years and above who accompanied women with breast cancer diagnosis, and residents of Addis Ababa were interviewed. Also, health care providers who had a minimum of bachelor degree in health sciences, and provided care to cancer patients at the oncology clinic for more than a year were included in the study.

3.4. Sample size determination

Sample size was determined according to the objectives and design of each of the papers. For **papers I, III and IV,** sample size was computed considering the type of the outcome variable and main explanatory variable using Open Epi™ epidemiologic calculator and/or STATA™ version 13. The sample size estimation for each of the papers is described below.

For **paper I,** sample size was determined using a single population proportion formula (formula 1) taking the expected proportion (p=35.0%) of patient delay (>3 months) and proportion (p=41.8%) of diagnostic delay (>1 month) from a similar study [69]. The single population proportion formula is described as follow.

$$n = \frac{(Z_{\alpha/2})^2 p(1-p)}{d^2} \text{---------- (1)}$$

Where:

p = The estimated proportion of patient/diagnosis delay

$Z_{\alpha/2}$ = Corresponding z score for a significance level of (1 - α) %

D = Desired precision (margin of error)

Assuming a 95% level of confidence, a 5% precision and a 5% non-response rate, a minimum of 368 and 393 women with breast cancer were required to estimate the magnitude of the patient and diagnostic delay, respectively. Also, we estimated the minimum sample size required to address the factors associated with the patient or diagnostic delay using a two population proportion formula (Formula 2). The two population proportion formula used was:

$$n = \frac{\left\{ Z_{\alpha/2}\sqrt{\frac{P(1-P)}{r}} + z_{\beta}\sqrt{P_1(1-P_1) + \frac{P_2(1-P_2)(1-r)}{r}} \right\}^2}{(P_2 - P_1)^2(1-r)} \text{---------- (2)}$$

Where:

$Z_{\alpha/2}$ = Corresponding z score for a significance level of (1 - α) %

Z_{β} = Corresponding z score for power (1-β)

r = Ratio of unexposed to exposed,

P = Pooled proportion= $(P_1 + rP_2)/(1+r)$

P_1 = Proportion of outcome among population with the exposure of interest

P_2 = Proportion of outcome among population without the exposure of interest

The estimation was done taking traditional medicine use as one of the main determinants of patient and diagnostic delay [58, 69]. The sample size computation was made with the inputs of a 95% confidence level, 80% power, and one to one ratio between those women who used

traditional medicine and those who do not. Taking the proportion of patient delay among traditional medicine users (P_1=64%) and among non-users (P_2=50.0%) [69], the calculated sample size was 392. While taking the proportion of diagnostic delay among traditional medicine users (P_1 = 72.0%) and among non-users (P_2 = 50.0%) [69], the calculated sample size was 154. However, to increase the precision of the estimates and power of the study, all available 441 women newly diagnosed for breast cancer and aged ≥18 years enrolled in the cohort were considered in the analysis.

For **paper II**, 23 In-depth Interviews (IDI) were conducted: 13 women with breast cancer, 5 family members, and 5 health care providers. Those women aged 18 years and above, diagnosed with primary breast cancer in 2016 and attended at the oncology clinic, capable of making the interview and residents in Addis Ababa city for more than 6 months before diagnosis. Similarly, family members aged 18 years and above who accompanied women with breast cancer diagnosis in 2016, and residents of Addis Ababa were included. Also, health care providers who had a minimum of bachelor degree in health sciences, and provided care to cancer patients at the oncology clinic for more than a year were included in the study. The sample size was determined based on information saturation; recurrent patterns became evident in the participants' narrations [133].

The sample size for **paper III** was estimated using the double population proportion formula (formula 2) considering symptom interval, time interval from symptom recognition to date of diagnosis [21, 58] as the main exposure variable associated with advanced-stage at diagnosis that provides the maximum sample size. Taking proportion of advanced-stage at diagnosis (P_1=52.0%) among women with symptom interval of ≤ 6 months and proportion of advanced-stage at diagnosis (P_2=69.0%) among women with symptom interval of > 6 months [21], 95% confidence level, 80% power and one to one ratio between the two populations; the calculated sample size was 260. To increase the power of the study, we have included all the women with known American Joint Committee on Cancer stage (n=406) excluding those with unknown stage and those whose stage was only documented after neoadjuvant treatment.

For **paper IV**, the sample size was estimated using the formula in Stata version 13 for the Cox model comparing survival curves between two groups under the Cox Proportional Hazard model. Taking 95% confidence interval, 80% power, 1.5 hazard ratio of failure among women with symptom interval of >3 months [23], 47.0% overall probability of an event (failure) [18], and 5% proportion of lost to follow-up; the total sample size was 428. To increase the power of the study,

we have included all the 441 women with breast cancer, which were part of the broader project [125]. However, 2 of them have no valid follow-up and treatment related data. Hence, in this analysis, we have included 439 women with invasive breast cancer.

3.5. Sampling methods

For **papers I, III and IV**, an eighteen months' cohort of women newly diagnosed with breast cancer were enrolled sequentially from the seven health facilities in Addis Ababa city, and the monthly report of Addis Ababa cancer registry cancer notification form. All women newly diagnosed with breast cancer were identified from the selected health facilities and approached to participate in the study (Figure 3). Besides, eligible women who were not captured in the seven health facilities were identified from the monthly report of the Addis Ababa cancer registry cancer notification form and contacted to participate in the follow-up study.

In **paper II**, the participants were selected through a purposeful specifically criterion sampling technique [134]. Participants were those breast cancer patients or family members accompanying women diagnosed for breast cancer in 2016, capable of making the interview and residents in Addis Ababa city for more than 6 months before diagnosis. The study also included health care providers who had a minimum of bachelor degree in health sciences, and provided care to cancer patients at the oncology clinic for more than a year were included in the study.

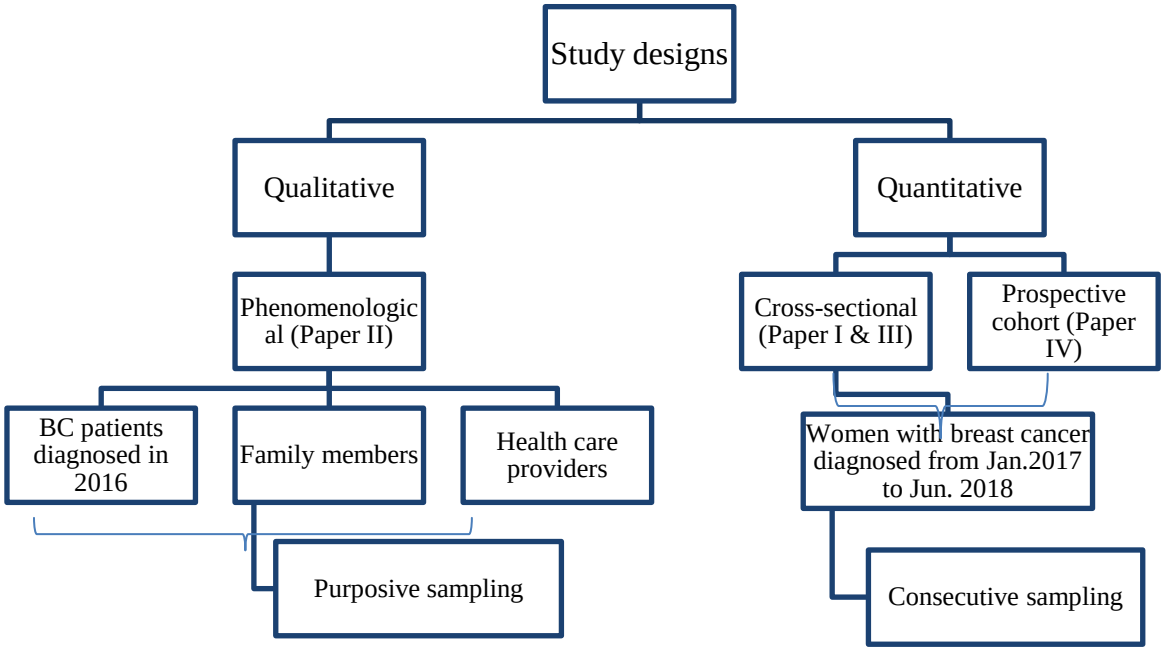

Figure 3: Summary of study designs, study participants and sampling methods of the dissertation, Addis Ababa, Ethiopia

3.6. Data collection tools and techniques

Three data collection tools were used to address the specific objectives of the dissertation. These are structured questionnaire, in-depth interview guides, and data extraction tool.

For **paper I**, data about the socio-demographic variables (e.g. age at diagnosis, highest attained-education, and occupation), date of first symptom/sign detection, method of initial detection, first symptoms recognized, date of first medical care sought, family history of breast cancer, breast cancer screening practices before first symptom recognition, self-reported chronic diseases and use of traditional medicines were obtained using an interviewer-administered questionnaire (Annex II, Part I). The date of diagnosis was taken from the patient's pathology report, The questionnaire was adapted with modification from a similar study conducted in Rwanda [58]. The questionnaire, which was pretested for cultural appropriateness and clarity, was developed in English then later translated and finalized in Amharic.

Thirteen nurses working in the selected health facilities were recruited for the data collection. We used health professionals working in the facility who had experience of working with cancer patients to address the questions or concerns raised by the patients during the interview. Also, the recruitment of the study participants was on daily basis and require full time worker and stayed for long period (18 months duration). The data collectors were at least diploma graduates from recognized institutions. One full-time master's degree holder was recruited for supervising the data collection process. Two days of training on the project's objectives and data collection procedures were provided to both the data collectors and supervisor. The trained nurses interviewed in Amharic the eligible women individually in a semiprivate room when they presented for treatment (at the time of recruitment to the study).

For **paper II**, semi-structured interview guides were used to interview the three groups of respondents: women with breast cancer, family members, and health care providers. Different interview guides were used for the three groups of participants (Annex III). The interview guides consisted of open-ended questions. For instance, some of the items in the breast cancer patients' interview guide were: "What is known about breast cancer in your community? Have you ever heard of breast cancer before you recognized the first symptoms of your illness? Tell me about your experience with breast cancer from the recognition of first symptoms to diagnosis? What are the major challenges you have faced during diagnosis? Why do women with breast cancer seek

medical care late? In addition to these main questions, the interview guide included probing questions.

Eligible participants were identified with the help of the head nurse of the oncology clinic. Interviews were conducted face to face with participants individually in a private room, either in the cancer registry office or head nurse's office of the oncology clinic. The primary investigator (AG) and three public health experts who had a Master in Public Health and experienced in qualitative research conducted the in-depth interviews. The four interviewers (2 males and 2 females) were paired into two groups consisting of one note taker and one interviewer. All of the in-depth interviews were taped. Each of the interviews took 40 minutes on average.

For **paper III**, a data extraction tool was used to abstract the stage at diagnosis and other clinical data from the medical charts of the patients. The abstracted data include date of diagnosis, tumor histology, grade, hormone receptor status, human epidermal growth factor 2, surgical margin involvement, lympho-vascular invasion, and clinical tumor size (Annex II, Part III). Data was extracted at about one year after the recruitment of the study participants to the follow-up study. For patients whose T, N and M data was not found in their medical chart, we used the available summary stage information. Senior oncology residents did the extraction. While the explanatory variables, such as time intervals (from symptom recognition to diagnosis), and socio-demographic characteristics of participants, were obtained through a face to face interview with the study participants using a structured interviewer-administered questionnaire (Annex II, Part I) during recruitment of the study participants to the project, as detailed in **paper I**.

Paper IV, in addition to the data obtained from the interviewer-administered questionnaire done during participant recruitment and clinical data extracted from the medical charts. Also, face-to-face interviews and telephone interviews conducted at about one and two years after recruitment to the study to capture the treatment and survival status. A face-to-face interview was conducted with the eligible participants by trained interviewers around one year after the recruitment. For those who were living in a physically inaccessible place, a telephone interview was done to capture data related to treatment status and survivorship concerns (Annex II, Part II). For patients who died or were too ill to be interviewed, a surrogate (next of kin) familiar with their cancer care was interviewed. Phone calls were made at least three times at different times of the day, evening, and weekends to increase the response rate of the study participants. If these efforts proved unsuccessful, the patient was considered as lost to follow-up [135]. Participants' survival

was assessed after two years since diagnosis using card review and/or phone interviews (Figure 4).

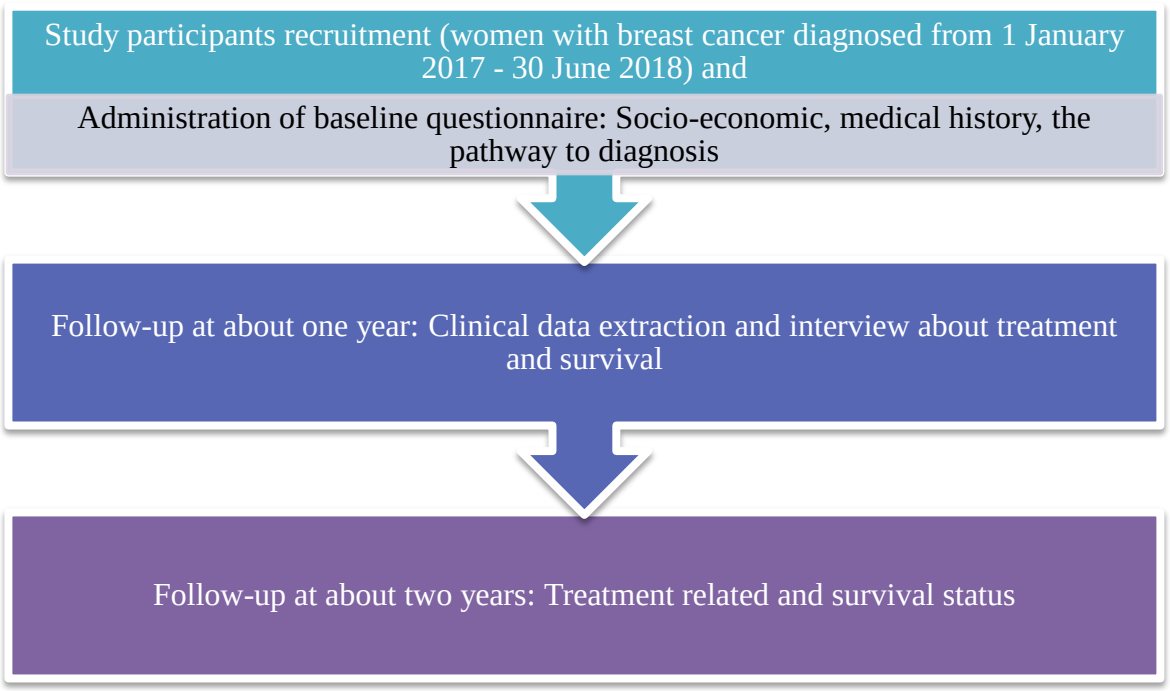

Figure 4: Flow chart of the study participants recruitment process, timing and type of data collected to address papers I, III and IV, Addis Ababa, Ethiopia

3.7. Study variables and measurements

The primary dependent variables of the quantitative study were time intervals from symptom recognition to diagnosis (**Paper I**), stage at diagnosis (**Paper III**), and death (**Paper IV**). A detailed description of the measurements of the primary outcome of each of the papers is given below.

Time interval: It refers to the time interval experienced by women with breast cancer from recognition of first symptom to date of pathologic diagnosis. The time intervals were categorized as patient interval, diagnostic interval [63], and symptom interval [21], treatment interval [63], and total interval using time as a classification criterion [76].

Patient interval: It refers to the interval from the date of first symptom recognition (the time point when first bodily changes and/or symptoms are noticed) to the date of first clinical presentation (the date at which the patient first presented to a health care provider after first recognition of symptoms) [63]. Symptoms refer to an abnormality noticed by the women or health care provider for the first time at her breast or axillary, which could include breast or

axillary mass, pain, nipple discharge, skin color, or texture change [136]. Those patients in whom breast abnormalities were first identified by physicians or mammography were excluded from our computation of patient interval (n=24). Patient delay was considered if the patient interval exceeds three months to initial consultation with the first health care provider [27, 60].

Diagnostic interval: It refers to the time interval from the date of first clinical presentation to the date of pathologic diagnosis. Date of pathologic diagnosis was the date at which first histological or cytological confirming invasive cancer reported [63]. The date of diagnosis was taken from the patient's pathology report. Data about the date of first symptom recognition and first medical consultation were obtained via the interviewer-administered questionnaire interview. Diagnosis delay was considered if the woman waited for more than a month [69, 71] since it has been associated with an increased risk of advanced-stage at diagnosis [101].

In the analysis of association between diagnosis delay and advanced-stage at diagnosis, diagnosis delay was modeled at two cut-points: $\leq$ 1 month versus > 1 month, and $\leq$ 2 months versus > 2 months. But we reported the model with two months cut-point of diagnosis delay since the modelling results at this cut-point explained the association between diagnosis delay and advanced-stage at diagnosis better than at 1 month cut-point.

The median length of time (IQR) between diagnosis and recruitment to the study/interview was 30 (10 to 73.5) days. If the patients were unable to recall the exact date of first symptom(s) experienced and date of the first consultation with a health care provider, such dates were approximated by probing the exact week of the respective month and year of symptoms experienced and the first medical consultation. If the participants were unable to recall the exact date of first symptom recognition, they were asked to provide a month or year ('was it at the beginning, middle, or end of the year?'). If the participants only said the beginning, middle, or end of the year, the estimated date was 15th of February, June or October of the year, respectively. These months were chosen because the participants mostly mentioned these months when probed to mention what beginning, middle, or end of the year is. For those who were only able to provide the year, the estimated date was June 30th of that year [58]. The detail is described in **paper I**.

Symptom interval: It refers to the time interval from first symptom(s) recognition to the first date of diagnosis [21]. We used this sub-interval to estimate the delay experienced between

symptom recognition and diagnosis, as well as to assess its effect on stage at diagnosis and overall survival.

For the survival analysis, the symptom interval was categorized as $\leq$ 3 months and >3 months to ensure comparability with previous study [23]. While in the association with stage at diagnosis, symptom interval was modelled as a three-level variable (<3 months, 3-6 months, and >6 months) to show the distribution of the magnitude of advanced-stage disease across the categories and guarantee comparability with a previous study [21].

Treatment interval: It refers to the time interval from the date of diagnosis to the date of the first treatment initiation [63]. The initiation of breast cancer treatment refers to the start of the first course of therapy and was obtained from the patients' medical chart if not from the patients' self-reports during the one- and two-year follow-up interviews. Women with unknown date of initial treatment, and those who refused recommended treatment were excluded from the analysis.

Total interval: It refers to the time interval from first symptom(s) recognition to the first treatment initiation [63].

In addition to the treatment initiation interval, we calculated the time to initiation of adjuvant chemotherapy and radiation therapy. Time to initiation of adjuvant chemotherapy refers to the number of days experienced between definitive breast cancer surgery and initiation of adjuvant chemotherapy [84, 137]. It was computed for those women with non-metastatic breast cancer (stage I, II, and III) who had a documented date of surgical treatment and date of initiation of adjuvant chemotherapy. Women who waited for >90 days were considered delayed [84]. We excluded those patients diagnosed with stage IV disease, who did not receive surgery or chemotherapy, had unknown date of surgery or chemotherapy, received neoadjuvant chemotherapy or radio-chemotherapy, or their stage information was missing.

Time to initiation of radiotherapy refers to the time interval between completing adjuvant chemotherapy and initiation of adjuvant radiotherapy. It was computed for those women who had documented dates of adjuvant chemotherapy completion and dates of initiation of adjuvant radiotherapy. Women with missing dates, those who took radio-chemotherapy, neoadjuvant chemotherapy or palliative radiotherapy were not included in the computation of radiotherapy waiting intervals.

Stage at diagnosis: The stage at diagnosis was abstracted from patient medical charts. Our analysis was based on clinical staging rather than pathologic staging because of lack of information on tumor characteristics, especially the nodal status, from pathology reports [138]. The staging was done according to the 7th edition of the AJCC Breast Cancer Staging Manual using the Tumor Node and Metastasis (TNM) system [49] into stage I, II, III, and IV. For patients whose T, N, and M data was not found in their medical chart, we used the available group stage information. All staging information done within the first 4 months after primary diagnosis in the absence of disease progression was used. We further dichotomized into a binary variable as early stages (I and II) and advanced-stages (III and IV) [10, 26].

In addition to the clinical staging, for the women who had primary surgical management, the axillary lymph node status was categorized as pN0, pN1, pN2, and pN3, and pN+ and pNx. Of those women with 10 or more lymph nodes examined, the number of positive lymph nodes on histopathological examination was classified into pN0 (no positive lymph node), pN1 (1–3 positive lymph nodes), pN2 (4–9 positive lymph nodes), and pN3 (≥10 positive lymph nodes). For those women with ≤9 lymph nodes examined, if any involved nodes were identified, these patients were classified as node-positive (pN+) or otherwise classified as lymph nodes that could not be assessed (pNx) [138]. Also, we calculated the lymph node ratio (LNR), defined as the ratio of positive lymph nodes to the total number of lymph nodes examined, and categorized into low (≤0.20), intermediate (0.21-0.65), and high-risk (>0.65) LNR groups [139].

Other tumor characteristics were also abstracted: Histological grade of breast cancer coded according to the Nottingham Grading System (1-well differentiated, 2-moderately differentiated, 3-poorly differentiated), tumor size categorized as per the AJCC guidelines (≤2 cm, >2–5 cm, >5 cm), margins (clear or involved), histology type (ductal, lobular, mixed, others), lympho-vascular invasion (negative or positive), and receptor status determined (yes/no).

Death: The study participants were followed from the date of diagnosis with invasive breast cancer until the date of last contact, the date of death, or until the end of the study (31 December 2019), whichever occurred first. Death from all causes was obtained either from the medical charts of the patients or through a phone call to the next of kin. The last status determination was done at about two years after the recruitment of the study participants. Participants who remained alive at the date of the last follow-up (31 December 2019) were censored. Two of the women were lost from the study within a month of follow-up, and excluded from the analysis. Another 2

women were lost after 16 months and 17 months follow-up, respectively, and were censored for the one-year survival but considered as a lost to follow-up for the two-year survival estimation. The overall survival was computed as the duration in months from diagnosis to death due to all causes [140-141]. Also, we computed the overall survival from the date of first symptoms recognition to last date of follow-up or death.

We defined some of the explanatory variables as follows. We categorized age into <40 years, 40-59 years, and ≥ 60 years; educational attainment into not attended formal school, primary school (grade 1-8), secondary school (grade 9-12), and some level of college education (>12 years of schooling); marital status into married and unmarried (single, widowed or divorced); participants job into "Yes" for those who had an outdoor job (employed, daily laborer or sellers) and "No" for those who had no outdoor job (housewives, retired or had no job) at the time of enrolment to the follow-up study. According to seven federal tax bracket categories, family monthly income was collected as categorical variables, then categorized into <61.0 United States Dollar (USD), 61.0-194.0 USD, and >194.0 USD during analysis. Ever practice of breast self-examination before symptom recognition was considered if the women responded "Yes" to the question "Before you feel/saw the first symptom/sign of your breast problem, did you ever examine your breast using your hand for lumps regularly?" The means of symptom detection was classified into self-detected (if detected by the women, her husband, or other family members) and health care provider detected (if first detected by health care providers' while the women visited for other health services or breast cancer screening). Before the first medical consultation, traditional medicine use was considered if the woman's primary response to the first symptom was using holy water, visiting traditional healers, or performing different ritual activities. At the same time, traditional medicine use before diagnosis was defined if they used traditional medicine after the first symptom recognition but before the diagnosis of breast cancer. We categorized the first health facility where participants visited for their first symptoms: health centers, public hospitals, and private hospitals/clinics. We dichotomized the number of health facilities visited before diagnosis into ≤3 and ≥4. The above variables were captured from face-to-face interviews during the women's recruitment to the follow-up study by trained interviewer.

The standard breast cancer treatment includes surgery, chemotherapy, radiotherapy, and hormonal therapy. Trained oncology residents systematically extracted treatment status (type of treatment given, date of treatment initiation), recurrence after treatment initiation, haemoglobin

level during diagnosis and after treatment, and documented comorbidities from the patients' medical charts. Extraction was done about one year after diagnosis and updated at the end of the follow-up, December 2019. We categorized surgical treatment as mastectomy (includes modified radical mastectomy and simple mastectomy), lumpectomy, or unknown. Chemotherapy was grouped as neoadjuvant, adjuvant, unspecified in its timing, and anthracycline-based only, anthracycline + taxane, and unspecified in its type of chemotherapy administered. The receipt of radiotherapy was classified in terms of its aim as an adjuvant, palliative, and unspecified. Hormonal therapy status was classified as yes, no, or unspecified, and types of hormonal therapy received first categorized as tamoxifen only, anastrozole, letrozole, and unspecified. The number of comorbidities (self-reported and from the medical chart) was dichotomized into "No" or "Yes" (if present > = 1). Hemoglobin level was categorized into <12.0 g/dl, ≥12.0 g/dl, and not specified.

3.8. Data management and analysis

3.8.1. Data quality assurance

Various actions were taken to maintain the quality of the research, starting from designing the tool to data analysis and interpretations of the findings. Briefly, it is summarized for each of the papers as follows:

For **papers I, III and IV**, all interviews were administered in Amharic, the country's working language. To ensure the accuracy of the questionnaire in Amharic, the tool was back-translated to English by individuals who were not familiar with the survey. The questionnaire was reviewed by local and international experts on the research subject and cancer care to improve the validity of the questions. Further, a pretest was performed to enhance the clarity of the data collection tools.

Data collectors and supervisor were recruited by considering their level of education and data collection experience. A data collection training manual was developed. Two days training about the purpose and procedure of the study were offered for the data collectors and supervisor. The training focused on how to select eligible study participants, what to do if the respondents are not volunteering at the time of first contact or refuse to co-operate, and instruction sheets on how to ask specific questions and how to record the answers. Besides, they trained on interview techniques, such as objectively asking questions, not showing by words or expressing what answers one expects, not showing agreement, disagreement or surprise, and recording the

answers precisely as they are provided, without shifting or interpreting them. The training included practical demonstration and in the field observation during the pre-test. Also, one day of debriefing about the clarity of the questions, interviewing techniques, and challenges faced during the pretest was discussed with the data collectors. In addition, continuous supportive supervision was provided throughout the data collection process. Data enumerators were told strictly to check the completeness of the questionnaire before concluding the interview. The supervisor verified the completeness of filled questionnaires on a daily basis. The researcher also reviewed the completeness and consistency of the data during data entry to the data manager, Epi-info™.

Biweekly meeting was held among the data collectors' supervisor, investigator, advisors, and project funders to discuss the number of cases recruited over two weeks, and solve any problems encountered during the data collection. The clinical data were abstracted by the experts, oncology residents, with close observation by the clinical supervisor (Dr. Mathewos Assefa, Oncologist).

Pre-designed templates with appropriately programmed skipping patterns using Epi-Info™ version 3.5.1 was used. To minimize data entry errors, data entry was done by the principal investigator. After the entry was completed, samples of the entered questionnaires were verified against the hard copy, and necessary corrections were made before the analysis. Missing values, outliers, and data entry errors were checked, and necessary corrections made accordingly. Women with outliers of patient and diagnosis intervals were re-contacted to verify the date of first symptom(s) recognition and first medical consultation.

For **paper II**, the qualitative data's trustworthiness was ensured through the following different measures taken from participant selection to analysis of the data. Both the primary investigator and data collectors were trained in qualitative research, and had experience in qualitative data collection and analysis. In addition, the supervisors of the primary investigator were also qualitative study experts. Moreover, inclusions of different groups of participants (breast cancer patients, family members, and health care providers) helped to triangulate and increase the credibility of the findings. The data collectors and investigators were debriefed daily to discuss themes and issues for exploration and to verify saturation of information. The content of the transcripts was verified with the audio records. Audio records of participants', notes taken during the interviews and verbatim transcriptions were saved for cross-checking the process and

sustained the consistency of the interpretations. Computer-based data coding, NVivo^{TM} software version 11, facilitated the reduction of qualitative data without missing the central idea.

3.8.2. Data analysis

For **papers I, III and IV,** cleaned data were exported for further analysis to Stata^{TM} 13 (StataCorp, LP, Texas, United States). Descriptive analyses were carried out for each of the study variables. Categorical variables are presented as counts and percentages. Numeric data were checked for normality using normality plots (Q-Q plots and/or histograms) and normality tests (Kolmogorov-Smirnov test). We used means with their standard deviation (SD) for those with normal distribution, and median and interquartile range (IQR) for those variables with skewed distributions. For instance, the distribution of number of days experienced from symptom recognition to treatment initiation was not normally distributed. As a result, we reported the median days with the IQR of the intervals. Results were presented in texts, tables, and graphs. Estimates of population parameters were presented with a 95% confidence interval (CI). Variables associated with the outcome at p-value <0.25 [142] on bivariate analysis, and those variables reported as having an impact on the outcome in the literature were included in the multivariable models.

In all of the multivariable analyses, presence of multicollinearity was checked using variance inflation factors (VIF < 10, as a cut of point). Variables for the multivariable regression models were fitted using the "enter" method. The goodness of fit of the Poisson regression with robust variance was checked using Pearson chi-square and deviance tests. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

For **paper I**, to determine the magnitude of patient and diagnosis delay among women with breast cancer, a descriptive analysis was used. The proportion of patients who spent more than three months before seeking medical care with its 95% CI was computed [27, 60]. Similarly, the proportion of patients who spent more than a month (time from first medical care sought to the time of diagnosis) before diagnosis with its 95% CI was computed. Also, multivariable Poisson regression with a robust variance, which gives prevalence ratio estimates, was used to determine the factors associated with patient and diagnosis delay since the proportion of experiencing the outcome was >10% [143-144], odds ratio my overestimate the effect measure. The detail is described in **paper I**.

For **paper III**, the proportion of advanced-stage (stage III and IV) at diagnosis was calculated based on all breast cancer patients with known stage disease. Since our outcome, advanced-stage at diagnosis was not rare in our sample population (64.3%), we used Poisson regression with a robust variance to directly estimate prevalence ratios and facilitate the interpretation of results as prevalence ratios rather than odds ratio [143-144]. Bivariate analyses were done for each of the independent variables with the binary outcome variable, advanced-stage at diagnosis. Then multivariable Poisson regression with robust variance was run to assess the association between advanced-stage at diagnosis and different patient characteristics. Before fitting the Poisson regression model, the model's assumptions, like the absence of multicollinearity among the independent variables, the presence of outliers, and model fitness, were checked.

For **paper IV**, the overall survival rate of two years was estimated using the Kaplan-Meier method and compared using the log-rank test. In addition, bivariate Cox regression analyses were performed to identify factors associated with the overall survival rate of women with breast cancer. Multivariable Cox proportional hazards model was run to compute the adjusted hazard ratio (aHR) of each of the determinants in the model. The proportional hazards assumption was checked using the graphical method and goodness of fit test, which were all satisfied.

For **paper II**, audio data were transcribed verbatim into Microsoft Word files and translated from the local language to English. Before the analysis, the audio recordings were listened repeatedly; as well transcribed texts were read multiple times and thoroughly to gain an in-depth understanding of the respondents' experiences. Verbatim transcripts of the data were imported into NVivo^{TM} software version 11 for computer-based data coding and reduction without compromising the central idea. Line-by-line coding was then done by the primary investigator. The coding was done thoroughly for the whole transcript. The various codes were compared based on differences and similarities, and identified patterns among the codes, finally grouped to themes. Accordingly, the analysis comes with eight dominant themes. An inductive method was used to determine the themes from the data obtained from the study participants. Through thematic analysis, then contents were analyzed for emerging themes and sub-themes [145]. The findings presented in terms of the dominant themes. Quotes that best described the various categories and expressed what was said frequently in several groups were chosen and presented in italics to ensure the comfirmability of the descriptions. The source of quote is presented by the code of each respondent type followed by the number of the respondent.

3.9. Ethical considerations

Before data collection, ethical clearance was obtained from the Institutional Review Board (IRB) of College of Health Science (018/17/SPH) of Addis Ababa University. A letter of support was also obtained from the Addis Ababa Health Bureau and other concerned bodies in the study area.

Eligible patients were verbally informed, by trained data collector, regarding the objectives and purposes of the study, and encouraged to ask questions to clarify any issues before commencement and to decide whether to participate in the follow-up study. Before they decided to participate, participants were informed that there were no wrong or right answers to the questions asked, and about the confidentiality and the period of the interview. Oral informed consent was obtained from quantitative study participants before their enrolment (Annex I). For the qualitative study, however, written consent was obtained from the study participants (Annex III).

The decision to use verbal consent for the participants of the quantitative study was made by a rapid ethical assessment that was conducted to design the consent process of this project [146]. Based on this assessment, we found that most of the participants were not comfortable providing written consent. Accordingly, we decided to use verbal consent, which was approved by the IRB of the College of Health Science of Addis Ababa University.

Participants were included if they clearly stated their willingness to participate in the study, including participation in the interview, use of medical records and possible phone contact for follow-up. Anyone unwilling to voluntarily participate was excluded from the study. During the interview, respondents interested in avoiding specific questions or discontinuing the conversation was allowed to do so.

Confidentiality of any information related to the participants and their clinical history was preserved. Information about their identity was put away after re-coding the file and kept in a secure place. All collected data were kept private and confidential. The hard copy and softcopy of every collected data were kept in a locked cabinet and password secured computer, respectively. Only the data clerk, physicians, and the investigators were able to link the participants' identity with the code number, should this become necessary to assist the participants medically. The transcriber and the principal investigator independently listened to all of the audio records of the

in-depth interviews. A specific code number was given to each of the participants. Only the codes, not the names of the respondents, were used in the write-up.

The research participants were told that the research project would not have any direct, immediate benefit to them. They were, however, informed that their participation is crucial to answer to the research question, which, in turn, benefits the society, especially women and their families. Participants received only transport allowance as compensation if they traveled for the interview, as this was not perceived as coercive in terms of their decision of participation and responses to the questions.

The study was interview-based and had no risk for the participants, and interviews were conducted in private rooms. The participants had the right to refuse or withdraw from the study at any time. Refusing to participate did not affect their treatment at the hospital or clinic in any way. During the training of data collectors, ethical issues were addressed as an essential component of the research.

3.10. Summary of the study objectives and methods

The summary of the objectives and methods used in the dissertation is shown in Table 1 below.

Table 1: Summary of objectives and study methods of the dissertation, Addis Ababa, Ethiopia

Paper	Study objectives	Study Design	Study subjects	Sample Size	Data collection tool	Data analysis
I	To determine the magnitude of patient and diagnostic delays	Cross-sectional study	Women Newly diagnosed for BC	368 and 393	Structured Questionnaire	Descriptive analyses
	To identify factors associated with patient and diagnosis delay	Cross-sectional study	Women Newly diagnosed for BC	154 and 392	Structured questionnaire	Multivariable Poisson regression with robust variance
II	To explore the reasons for late diagnosis of women with breast cancer in Addis Ababa city	Phenomenological study	Women with BC, Family members and HCP	23 IDIs	Interview guides	Thematic analyses
III	To identify the factors associated with advanced-stage at diagnosis	Cross-sectional study	Women Newly diagnosed for BC	260	Structured questionnaire Data extraction checklist	Multivariable Poisson regression with robust variance
IV	To determine two-year survival rate and its associations with delay and stage at diagnosis of women with breast cancer in Addis Ababa city	Prospective cohort study	Women Newly diagnosed for BC	428	Structured questionnaire, Data extraction checklist	Survival analysis Cox's regression

BC: Breast cancer, IDI: In-depth interview; HCP: Health care providers

As shown in the above Table 1, the largest sample size among those computed for the quantitative objectives was 428. Since cases recruited for the project on breast cancer patients' experience [125] were 441 and were followed for the vital status, this sample size were sufficing for all quantitative study objectives. Thus, to increase the power of the study and precision of the estimates, all available newly diagnosed women with breast cancer aged 18 years and above enrolled in the cohort (n=441) were considered for all of the quantitative objectives of the dissertation.

4. Results

4.1. Time intervals between first symptom recognition and treatment initiation of women with breast cancer

4.1.1. Socio-demographic characteristics of study participants

Of the 444 eligible participants approached, 441 (99.3%) provided informed consent to participate in the study. The mean (SD) age of the participants was 44.4 (12.2) years. More than two-thirds of the women diagnosed before their fifty years (Figure 5).

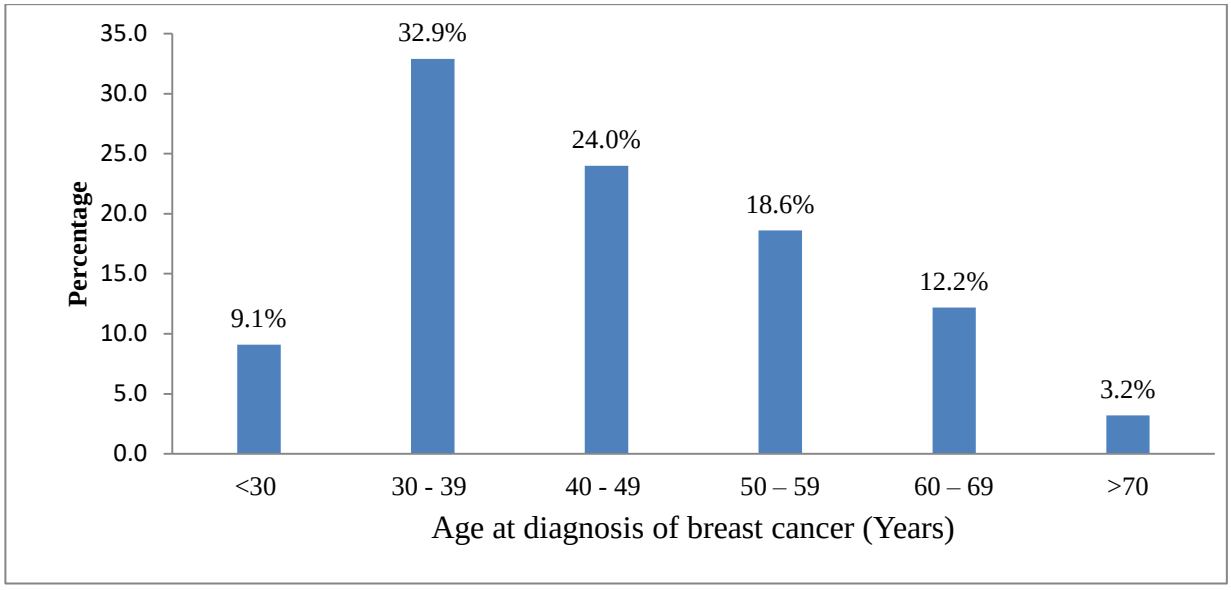

Figure 5: Age distribution of women with breast cancer diagnosed from 1 January 2017-30 June 2018, Addis Ababa, Ethiopia (n=441)

Table 2 shows participants' characteristics at the time of recruitment to the follow-up study. Fifty-eight percent of the women were married at the time of interview. Nearly half of the women were housewives (homemakers). More than a quarter (28.3%) of the participants reported a family income of less than US$ 61 per month; 71% of the participants paid their medical expenses out of pocket.

Table 2: Socio-demographic characteristics of women with breast cancer diagnosed from 1 January 2017-30 June 2018, Addis Ababa, Ethiopia (n=441)

Socio-demographic characteristics	Frequency	Percentage
Highest level of education		
Not attended formal school	87	19.7
Primary school (1-8th)	112	25.4
Secondary school (9-12th)	142	32.2
Diploma and above	100	22.7
Marital status		
Married	255	57.8
Widowed	73	16.6
Single	67	15.2
Divorced	46	10.4
Occupation		
Housewife (homemaker)	217	49.2
Employed outside the home	198	44.9
Retired	13	2.9
No job	13	2.9
Family size		
≤2	65	14.7
3-5	260	59.0
≥6	116	26.3
Family monthly income (US dollar*)		
<61.0	125	28.3
61.0-194.0	200	45.4
194.1-403.0	81	18.4
>403.0	25	5.7
Unknown	7	1.6
No income	3	0.7
Source of medical expenses		
Out of pocket	313	71.0
Free medical care	103	23.4
Health insurance	25	5.6

*1Ethiopian birr = 0.037 US Dollar (the exchange rate during participants enrolment to the study)

4.1.2. Pre-symptomatic breast cancer information and first symptom(s) appraisal

One-third of the women (32.2%, 95% CI [27.9%, 36.6%]) had never heard of breast cancer before noticing the first symptom of their illness. Fifty of the participants (11.3%) reported family history of breast cancer. Of those who heard of breast cancer, mass media was the main

source of information (72.9%), followed by family members or friends (24.4%) (Figure 6). Before recognizing the first symptom(s), 73%, 78.0%, 91.6%, and 94.6% of the study participants did not know how to do a BSE, had no history of BSE, CBE, and mammography breast examination, respectively.

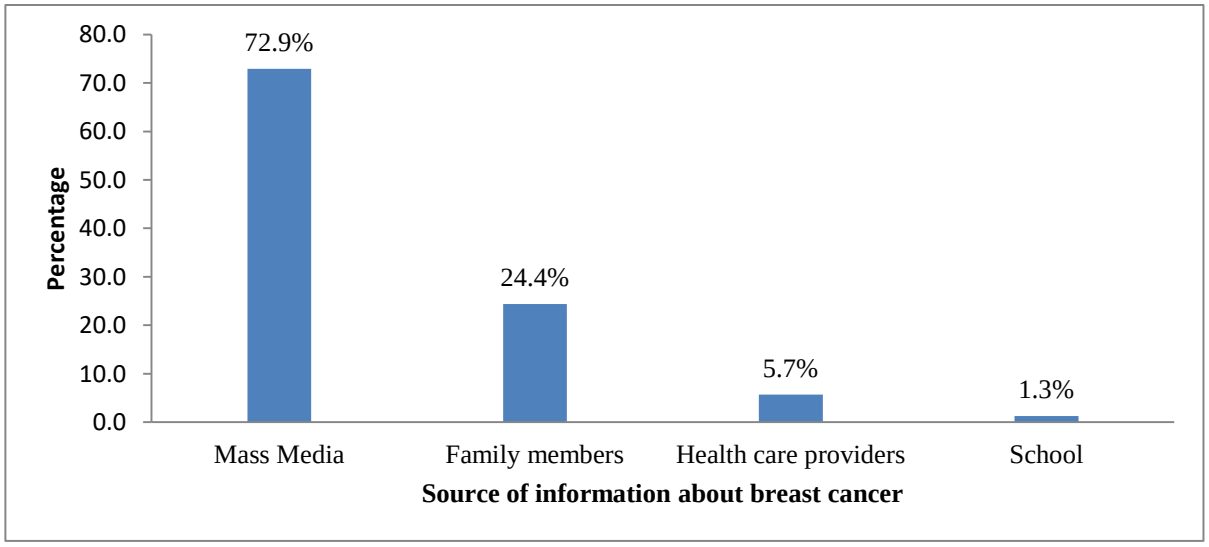

Figure 6: Pre-symptomatic source of information about breast cancer among women with breast cancer diagnosed from 1 January 2017 - 30 June 2018, Addis Ababa, Ethiopia
(More than one response was possible)

Ninety-five percent of the women's first breast cancer symptom(s) was self-detected, which was predominantly breast lump (78.0%) followed by pain (10.2%), change in color of the nipple (4.8%), and breast discharge (4.3%). Of the self-detected symptoms, only 8.0% of the women considered the first symptom(s) as possible cancer symptoms. More than a third (36%) thought it was a simple breast swelling, and 56.0% attributed to other causes (e.g., sunstroke, cold exposure, menses, and breast milk). The primary response of 13% of the women was using traditional medicines, such as holy water and visiting traditional healers. Remarkably, 19% of the participants did not seek medical care until they recognized the progression of their breast cancer symptom(s) (Table 3).

The primary triggers for seeking medical care were the first breast cancer symptom(s) (70.0%), followed by noticing the progression of symptom(s) (14.1%), and persuasion from family members/friends (13.2%). More than a third (36.2%) of the women first had their symptom(s) assessed at a health center, and 24.0% of the women visited ≥ 4 different healthcare facilities, while 23% of the women made ≥ 10 visits to healthcare facilities before the final pathologic diagnosis of their disease (Table 3).

Table 3: First symptom(s) appraisal and response of women with breast cancer diagnosed from 1 January 2017-30 June 2018, Addis Ababa, Ethiopia (n=441)

Variables	Frequency	Percentage
Means of first symptom/sign detection		
Self-detected	417	94.6
Health care provider detected	24	5.4
Participant's thought of first symptom/sign (n=417)		
Cancer	33	7.9
Breast swelling	150	36.0
Attributed to others**	234	56.2
Traditional medicine use before consultation (n=417)		
Yes	52	12.5
No	365	88.5
Progression of symptoms before consultation (n=417)		
No	337	80.8
Yes	80	19.2
***Types of symptoms progressed (n=80)**		
Breast lump	29	36.3
Discharge from the lesion and pain	29	36.5
Change in color of the breast	19	22.5
Nipple retraction	5	6.3
Others (neck or armpit pain, numbness)	8	10.0
Triggers to seek medical care (n=417)		
The first symptoms	292	70.0
Progression of symptoms	59	14.1
Family member/friends	55	13.2
HCP secondary to other care	11	2.7
Health facility of the first medical consultation (n=417)		
Public health center	151	36.2
Public hospital	97	23.3
Private hospital/clinic	169	40.5
Number of healthcare facilities visited before diagnosis		
≤3	335	76.0
≥4	106	24.0
Number of visits to healthcare facility before diagnosis		
≤3	126	28.6
4-9	212	48.0
≥10	101	22.9
Unknown	2	0.5

*Multiple responses were possible; **sun stroke ("mitch"), cold exposure, menses, breast milk; HCP: Health care providers

4.1.3. Magnitude of patient and diagnostic intervals

The median (IQR) patient interval was 30 (6 to 132) days. The magnitude of patient delay was 35.7% (95% CI [31.1%, 40.3%]); 11% of the patients waited for over a year (Figure 7). The main reasons for the patient delay were "*not bothered by the problem at first*" (69%), followed by using holy water/visiting traditional healers first (17.4%), and unable to take time off from work (12.7%) (Table 4).

The median (IQR) diagnostic interval was 69 (22 to 213) days. The magnitude of diagnostic delay was 69.1% (95% CI [64.6%, 73.3%]). Nearly one fifth (18%) of these women waited more than a year to receive diagnostic confirmation after their initial medical presentation (Figure 7). The most common reasons given by the women for their extended diagnostic interval (over a year) include both provider factors, such as misdiagnosis (25.6%) and false-negative laboratory results (3.8%), and patient factors, like use of traditional medicine (20.5%), fear of cancer diagnosis and treatment (especially breast surgery) (18.0%) and lack of awareness about disease severity (6.4%) (Table 4).

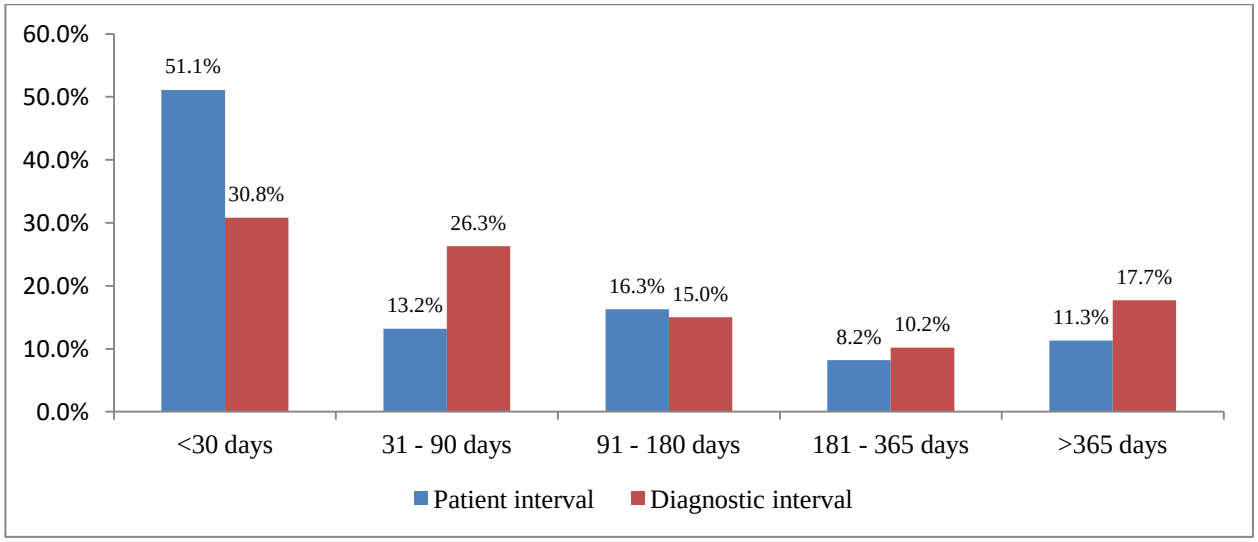

Figure 7: Patient and diagnostic intervals of women with breast cancer diagnosed from 1 January 2017- 30 June 2018, Addis Ababa, Ethiopia

Women who first visited health centers for their initial symptom(s) had higher median diagnostic interval (89 days) than those who first visited hospitals (55 days). Also, the median number of visits to healthcare facilities before diagnostic confirmation was higher among patients who first visited health centers (8 visits) compared to those who first visited public or private hospitals/clinics (4 visits).

Table 4: Main reasons for patient delay, and diagnosis delay among women with breast cancer diagnosed from 1 January 2017-30 June 2018, Addis Ababa, Ethiopia

Main reasons	Frequency	Percentage
Main reasons for patient delay (>3 months) (n=149) *		
Not bothered by the problem at first	103	69.1
Using holy water/ visited a traditional healer first	26	17.4
Being busy at home or job	19	12.7
Being a painless lump	17	11.4
Afraid of the treatments, mainly breast operation	9	6.0
Do not know where an appropriate medical facility was found	8	5.3
Do not want anyone knowing her breast problem	8	5.3
Afraid of being examined by a doctor or other health provider	6	4.0
Afraid of examination results	6	4.0
Thought treatment might be too expensive	3	2.0
Patients main reasons for diagnostic delay of > 1 year (n=78)		
Wrong diagnosis of the sign/symptoms	20	25.6
Traditional medicine use (traditional healers and holy water)	16	20.5
Fear of cancer diagnosis and treatment (breast surgery)	14	18.0
Time constraints	5	6.4
Lack of awareness about disease severity	5	6.4
A negative result from Ultrasound/Biopsy	3	3.8
Unhappy with the approaches of the physician at first contact	3	3.8
Financial constraints	3	3.8
Frustrated by the advice of the physician	2	2.6
Do not declare their reasons	7	9.0

*The percentages do not sum to 100 because multiple responses were possible.

Table 5 shows sensitivity analysis results of the patient and diagnostic intervals, with all study participants and excluding women who did not remembered the date of first symptom recognition or clinical presentation. Exclusion of those women who did not remembered the date of first symptom recognition or first medical consultations pooled the estimates to the lowest time intervals because they were more likely to be late presenters (have the highest waiting interval).

Table 5: Sensitivity analysis of the proportion of delays at different time intervals with all cases, and excluding those who do not remember the date of first symptom recognition or clinical presentation

Time intervals	All cases	After exclusion
	Proportion (95% CI)	**Proportion (95% CI)**
Patient intervals		
≤30 days	51.1% (46.2%, 55.8%)	63.7% (58.2%, 68.9%)
31-90 days	13.2% (10.2%, 16.8%)	16.5% (12.7%, 21.0%)
91-180 days	16.3% (13.0%, 20.2%)	10.3% (7.4%, 14.3%)
181-365 days	8.2% (5.8%, 11.2%)	5.1% (3.1%, 8.3%)
>365 days	11.3% (8.5%, 14.7%)	4.2% (2.4%, 7.1%)
Patient delay (>90 days)	35.7% (31.1%, 40.3%)	20.0% (15.9%, 24.9%)
Median patient interval (IQR)	30 (6 to 132) days	21 (6 to 60) days
Diagnostic intervals		
≤30 days	30.8% (26.7%, 35.3%)	35.6% (30.9%, 40.5%)
31-90 days	26.3% (22.0%, 30.6%)	29.0% (24.7%, 33.8%)
91 -180 days	15.0% (11.9%, 18.6%)	13.8% (10.7%, 17.7%)
181-365 days	10.2% (7.6%, 13.4%)	9.4% (6.8%, 12.8%)
>365 days	17.7% (14.3%, 21.5%)	12.0% (9.1%, 15.7%)
Diagnosis delay (>30 days)	69.1% (64.6%, 73.3%)	64.4% (59.4%, 69.1%)
Median diagnosis interval (IQR)	69 (22 to 213) days	56 (19 to 150) days

IQR: Interquartile range

4.1.4. Factors associated with patient and diagnostic delays

After adjustment to the variables with bivariate p-value of <0.25 and those reported in the literature as having an impact on patient delay, using traditional medicine before consultation (Adjusted PR=2.13, 95% CI [1.68, 2.71]) was the only factor significantly associated with an increased prevalence of patient delay (Table 6).

Besides the above variable selection criteria, we have also rerun the multivariable model at different bivariate p-value cut points (by including only those variables which were significant at p-value <0.2, another scenario at p-value <0.1, and the last scenario at p-value <0.05). But, traditional medicine use before consultation was the only variable that remained significantly associated with patient delay.

Table 6: Factors associated with patient delay (>90 days) among women with breast cancer diagnosed from 1 January 2017- 30 June 2018, Addis Ababa city, Ethiopia (n=417)

Patient characteristics	Patient delay		Unadjusted		Adjusted
	Yes (%)	No (%)	PR (95% CI)	P-value	PR (95% CI)
Age at diagnosis (years)					
<40	55(30.5)	125(69.4)	Ref.		Ref.
40-59	66(37.7)	109(62.3)	1.23(0.92, 1.65)	0.157	1.27(0.96, 1.69)
≥60	28(45.2)	34(54.8)	1.47(1.03, 2.10)	0.030	1.24(0.82, 1.87)
Family size					
≤ 2	22(36.6)	38(63.3)	Ref.		Not included
3-5	80(32.4)	167(67.6)	0.88(0.60, 1.29)	0.521	
≥6	47(42.7)	63(57.3)	1.28(0.78, 1.73)	0.450	
Participants' education					
Not attended school	40(51.3)	38(48.7)	2.19(1.42, 3.38)	0.000	1.52(0.91, 2.53)
Primary school	35(31.8)	75(68.2)	1.36(0.85, 2.16)	0.190	1.06(0.65, 1.73)
Secondary school	53(38.1)	86(61.9)	1.63(1.06, 2.51)	0.025	1.39(0.89, 2.16)
Diploma and above	21(23.3)	69(76.7)	Ref.		Ref.
Marital status					
Married	80(33.2)	161(66.8)	0.84(0.65, 1.09)	0.205	0.99(0.76, 1.27)
Single, widowed or divorced	69(39.2)	107(60.8)	Ref.		Ref.
Had outdoor job					
No	90(39.5)	138(60.5)	1.26(0.96, 1.64)	0.084	1.03(0.77, 1.38)
Yes	59(31.2)	130(68.8)	Ref.		Ref.
Partner's education (n=241)[c]					
Not attended school	13(54.2)	11(45.8)	2.04(1.22, 3.41)	0.006	Not included
Primary school	21(37.5)	35(62.5)	1.41(0.86, 2.31)	0.168	
Secondary school	24(30.7)	54(69.2)	1.16(0.71, 1.89)	0.551	
Diploma and above	22(26.5)	61(73.5)	Ref.		
Partner's employment (n=241)					
Employed	52(32.9)	106(67.1)	0.97(0.67, 1.42)	0.897	Not included
Not employed	28(33.7)	55(66.3)	Ref.		
Family monthly income					
<61.0 $	51(39.5)	78(60.5)	1.42(0.96, 2.08)	0.074	1.14(0.76, 1.72)
61.0-194.0 $	71(37.2)	120(62.8)	1.33(0.92, 1.93)	0.126	1.14(0.79, 1.65)
>194.0 $	27(27.8)	70(72.2)	Ref.		Ref.
Ever give birth					
No	28(34.5)	53(65.4)	Ref.		Not included
Yes	121(36.0)	215(64.0)	1.04(0.74, 1.45)	0.809	
Women's number of live children (n=336)[c]					
≤ 2	57(31.0)	127(69.0)	Ref.		Not included
3-4	41(38.7)	65(61.3)	1.24(0.90, 1.72)	0.178	
≥5	23(50.0)	23(50.0)	1.61(1.12, 2.31)	0.009	

Continued…

Table 6. Continued.

Patient characteristics	Patient delay		Unadjusted		Adjusted
	Yes (%)	No (%)	PR (95% CI)	P-value	PR (95% CI)
Ever heard of BC[a]					
No	58(43.3)	76(56.7)	1.34(1.04, 1.74)	0.024	1.17(0.89, 1.53)
Yes	91(32.2)	192(67.8)	Ref.		Ref.
Practiced BSE[a]					
No	123(37.9)	201(62.0)	1.35(0.95, 1.93)	0.091	1.15(0.81, 1.63)
Yes	26(28.0)	67(72.0)	Ref.		Ref.
Breast pain as the first symptom					
No	140(36.6)	242(63.4)	1.42(0.79, 2.54)	0.230	1.44(0.83, 2.50)
Yes	9(25.7)	26(74.3)	Ref.		Ref.
Painless lump as the first symptom					
No	27(32.1)	57(67.9)	Ref.		Not included
Yes	122(36.6)	211(63.4)	1.13(0.80, 1.60)	0.453	
Breastfeeding during symptom recognition					
No	135(35.1)	249(64.8)	Ref.		Ref.
Yes	14(42.4)	19(57.6)	1.20(0.79, 1.83)	0.381	1.38(0.93, 2.05)
Participant's thought of first symptom/sign					
Cancer	11(33.3)	22(66.7)	Ref.		Ref.
Breast swelling	46(30.7)	104(69.3)	0.92(0.53, 1.57)	0.762	0.78(0.46, 1.34)
Attributed to others	92(39.3)	142(60.7)	1.17(0.70, 1.96)	0.525	0.96(0.57, 1.61)
Traditional medicine use[b]					
No	112(30.7)	253(69.3)	Ref.		Ref.
Yes	37(71.1)	15(28.9)	2.31(1.83, 2.92)	0.000	2.13(1.68, 2.71)***

$US dollar; [a] before symptom recognition; [b]before medical consultation; PR: Prevalence ratio; BSE: Breast Self-Examination; [c]partner's education (n=241) and women's number of alive children (n=336) was not included in the multivariable model to maintain the power of the model. ***P < 0.001

After adjustment to the variables with bivariate p-value of < 0.25 and those reported in the literature as having an impact on diagnostic delay, diagnostic delay was significantly higher among women who had first consultation at a health center (Adjusted PR=1.19, 95% CI [1.02, 1.39]) and visits to $\geq$ 4 health facilities before diagnosis (Adjusted PR=1.24, 95% CI [1.10,1.40]). In contrast, it was lower among women who had consulted after they noticed progression of the first symptom (Adjusted PR=0.73, 95% CI [0.60, 0.90]) (Table 7). Besides the above variable selection criteria, we have also rerun the multivariable model at different bivariate p-value cut points (by including only those variables which were significant at p-value <0.2, another scenario at p-value <0.1, and the last scenario at p-value <0.05). But only the above three variables remained significantly associated with diagnostic delay.

Table 7: Factors associated with diagnostic delay (>30 days) among women with breast cancer diagnosed from 1 January 2017- 30 June 2018, Addis Ababa city, Ethiopia (n=441)

Patient characteristics	Diagnosis delay		Unadjusted		Adjusted
	Yes (%)	No (%)	PR (95% CI)	P-value	PR (95% CI)
Age at diagnosis (Years)					
<40	133(71.9)	52(28.1)	Ref.		Ref.
40-59	128(68.1)	60(31.9)	0.94(0.82, 1.08)	0.423	0.97(0.85, 1.11)
≥60	44(64.7)	24(35.3)	0.90(0.73, 1.09)	0.296	0.89(0.71, 1.11)
Family size					
≤ 2	47(72.3)	18(27.7)	Ref.		Not included
3-5	178(68.5)	82(31.5)	0.94(0.79, 1.12)	0.533	
≥6	80(68.9)	36(31.0)	0.95(0.78, 1.15)	0.633	
Participants' education					
Not attended school	60(68.9)	27(31.0)	1.02(0.84, 1.25)	0.774	1.02(0.84, 1.23)
Primary school	82(73.2)	30(26.8)	1.09(0.91, 1.30)	0.328	1.03(0.84, 1.26)
Secondary school	96(67.6)	46(32.4)	1.00(0.84, 1.20)	0.921	1.06(0.83, 1.35)
Diploma and above	67(67.0)	33(33.0)	Ref.		Ref.
Marital status					
Married	172(67.4)	83(32.6)	0.94(0.83, 1.06)	0.359	0.92(0.81, 1.04)
Single, widowed or divorced	133(71.5)	53(28.5)	Ref.		Ref.
Had outdoor job					
No	168(69.1)	75(30.9)	0.99(0.88, 1.13)	0.990	1.02(0.89, 1.17)
Yes	137(69.2)	61(30.8)	Ref.		Ref.
Partner's education (n=241)					
Not attended school	17(65.4)	9(34.6)	0.94(0.69, 1.29)	0.744	Not included
Primary school	41(71.9)	16(28.1)	1.04(0.84, 1.29)	0.692	
Secondary school	52(63.4)	30(36.6)	0.92(0.74, 1.14)	0.452	
Diploma and above	62(68.9)	28(31.1)	Ref.		
Partner's employment (n=241)					
Employed	110(66.3)	56(33.7)	0.95(0.79, 1.13)	0.576	Not included
Not employed	62(69.6)	27(30.3)	Ref.		
Family monthly income					
<61.0 $	96(71.1)	39(28.9)	1.10(0.92, 1.32)	0.258	1.03(0.84, 1.26)
61.0-194.0 $	141(70.5)	59(29.5)	1.09(0.92, 1.30)	0.272	1.06(0.89, 1.26)
>194.0 $	68(64.1)	38(35.8)	Ref.		Ref.
Ever give birth					
No	59(69.4)	26(30.6)	Ref.		Not included
Yes	246(69.1)	110(30.9)	0.99(0.85,1.16)	0.955	
Woman's number of alive children (n=336)					
≤ 2	136(69.7)	59(30.3)	Ref.		Not included
3-4	76(68.5)	35(31.5)	0.98(0.83, 1.14)	0.817	
≥5	34(68.0)	16(32.0)	0.97(0.78, 1.20)	0.815	

Continued…

Table 7. Continued.

Patient characteristics	Diagnosis delay		Unadjusted		Adjusted
	Yes (%)	No (%)	PR (95% CI)	P-value	PR (95% CI)
Source of medical expenses					
Out of pocket	211(67.4)	102(32.6)	0.99(0.74, 1.31)	0.952	0.97(0.73, 1.29)
Free medical care	77(74.8)	26(25.2)	1.09(0.82, 1.47)	0.524	1.09(0.81, 1.47)
Health insurance	17(68.0)	8(32.0)	Ref.		Ref.
Ever heard of breast cancer[a]					
No	104(73.2)	38(26.8)	1.08(0.95, 1.23)	0.187	0.95(0.83, 1.09)
Yes	201(67.2)	98(32.8)	Ref.		Ref.
Practiced BSE[a]					
No	236(68.6)	108(31.4)	0.96(0.83, 1.11)	0.626	Not included
Yes	69(71.1)	28(28.9)	Ref.		
Breast pain as the first symptom					
No	270(68.2)	126(31.8)	0.87(0.73, 1.03)	0.130	0.85(0.71, 1.02)
Yes	35(77.8)	10(22.2)	Ref.		Ref.
Painless lump as the first symptom					
No	68(70.1)	29(29.9)	Ref.		
Yes	237(68.9)	107(31.1)	0.98(0.84, 1.13)	0.818	Not included
Means of symptom detection					
Self-detected	291(69.7)	126(30.2)	Ref.		
Health care provider	14(58.3)	10(41.7)	0.83(0.59, 1.17)	0.308	0.77(0.53, 1.10)
Progression of symptoms[b]					
No	259(72.1)	100(27.9)	Ref.		Ref.
Yes	46(56.1)	36(43.9)	0.77(0.63, 0.95)	0.015	0.73(0.60, 0.90) ***
First medical consultation					
Public health center	122(77.7)	35(22.3)	1.25(1.08, 1.44)	0.002	1.19(1.02, 1.39)*
Public hospital	71(68.9)	32(31.1)	1.11(0.93, 1.32)	0.222	1.11(0.94, 1.32)
Private hospital/clinic	112(61.9)	69(38.1)	Ref.		Ref.
Number of health facilities visited before diagnosis					
≤3	218(65.1)	117(34.9)	Ref.		Ref.
≥4	87(82.1)	19(17.9)	1.26(1.12, 1.42)	0.000	1.24(1.10, 1.40) ***

$US dollar; [a] before symptom recognition; [b]before medical consultation; PR: Prevalence ratio; BSE: Breast Self-Examination, *p < 0.05, ***P < 0.001.

4.1.5. Treatment initiation and total intervals

The median symptom interval was 179 (IQR: 68 to 414) days (Figure 8). This duration exceeded three months for 68% of the women and over one year for about 30% of the women.

The median treatment interval was 29 (IQR: 9 to 58) days (Figure 8). Eighteen percent of the women received treatment after three months of diagnosis.

The median total interval was 213 (IQR: 81 to 471) days (Figure 8); only 28.4% of the women initiated treatment within three months of first symptom recognition. The total interval exceeded a year for 20.2% of the women.

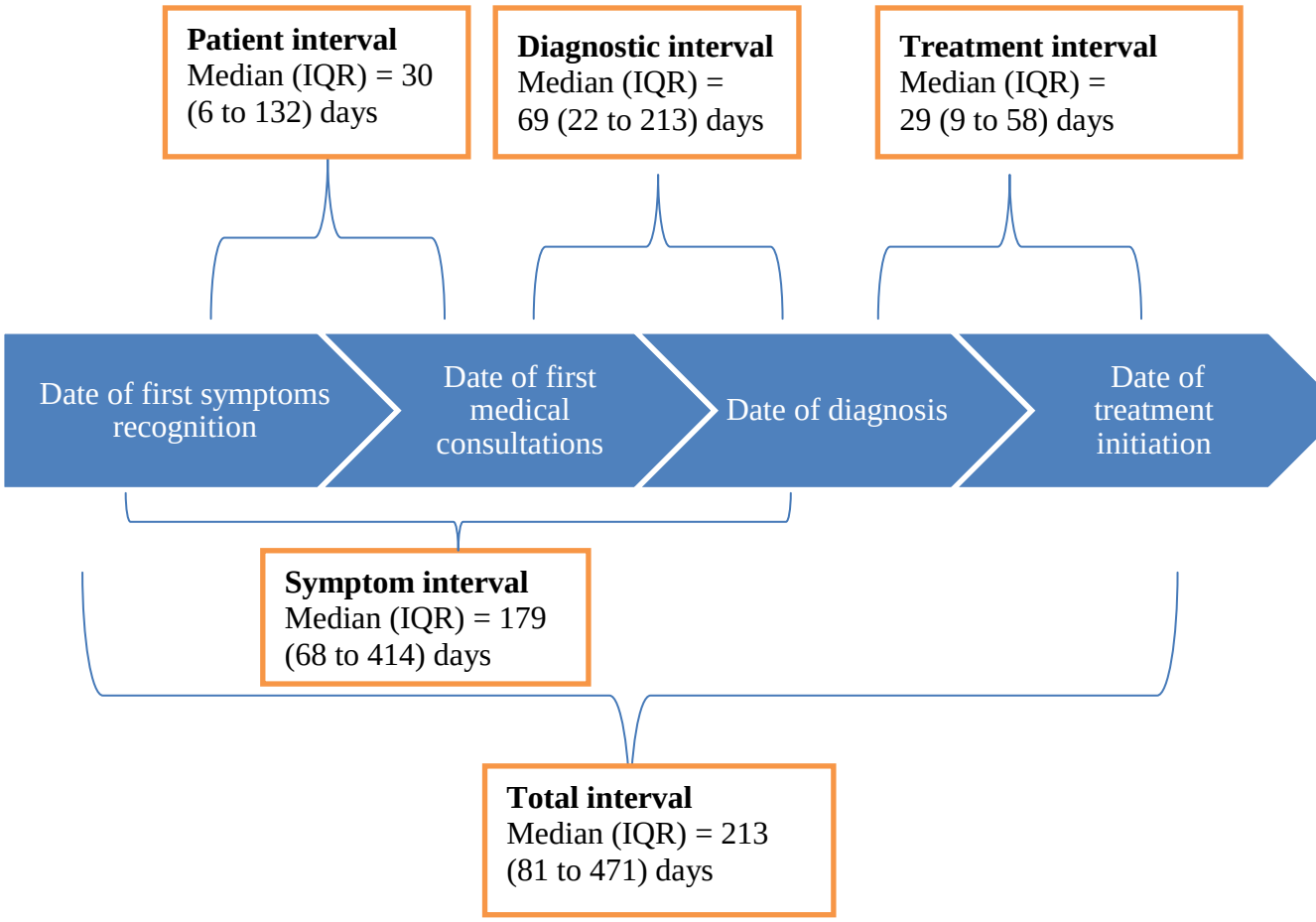

Figure 8**:** Median patient, diagnosis, symptom, treatment and total intervals of women with breast cancer diagnosed from 1 January 2017- 30 June 2018, Addis Ababa, Ethiopia

4.2. Perspectives of patients, family members, and health care providers on late diagnosis of BC

4.2.1. Study participants' characteristics

Qualitative study was done to explore reasons for late diagnosis of breast cancer. In-depth interviews were conducted with 13 breast cancer patients, 5 family members, and 5 health care providers of Tikur Anbessa Specialized Hospital Oncology clinic (Table 8).

Table 8: Qualitative study participants' characteristics, Oncology Clinic, TASH, Addis Ababa, Ethiopia, 2017

Participants' Characteristics	Breast cancer patients (P01-13)	Family members (R01-05)	Health care providers (HP01-05)
Participants age (years)			
<40	7	3	*
40-50	5	1	*
>50	1	1	*
Highest level of education			
Not attended formal school	7		
Primary school (1-8th)	5	1	
Secondary school (9-12th)	2	1	
Diploma and above	1	3	5
Occupation			
Homemaker (housewife)	2		
Employed	8	3	
No job	3	2	
Health care providers			5

P: Breast Cancer Patient; R: Family Member; HP: Health Care Providers, *the age of health care providers is omitted to keep anonymity

Based on thematic analysis, the responses of the participants revealed eight common reasons for late diagnosis, and three factors contributing to early diagnosis.

4.2.2. Reasons for late diagnosis of breast cancer

The main reasons for late diagnosis are summarized as follow.

1. **Lack of awareness about breast cancer in the community:** In all cases, the respondents reported that community awareness of breast cancer is low. They pointed out that breast cancer-related discussions and screening practices were uncommon in their community. A recurrent response among the women interviewees was, "*I had never heard of breast cancer before I sought care for my illness.*"

"Before I recognized the first symptom of my illness, I have never heard of breast cancer. Rather, I heard women say I have pain in my breast…" (P08)

"… People in my community are not aware of breast cancer or they have wrong information about cancer…" (HP04)

2. **Disregarding or misattribution of breast cancer symptoms:** In most of the patients, the first symptom was painless breast lump, which detected by the women accidentally. The painless nature of the lump made the women ignore its potential severity, usually attributing it to a non-cancer illness, mainly sunstroke, locally called "mitch." As one woman with breast cancer who first recognized a painless swelling reported, she ignored the lump for about a year without looking for any medical care. After she realized her nipple inverted, she became concerned and sought medical attention.

"I thought it was just a disease not as severe as this… I thought it was caused by the odor of the place I worked at… I thought it was something related to mitch …" (P02)

"I noticed a small swelling in my breast. But I was not worried about it. It started to extend its tail to my armpit. Then I went to the health center. They told me to go to the hospital… I did not trust them. I considered the disease as nothing. When I felt severe pain, I returned to the healthcare facility. The doctor became visibly angry at me." (P01)

3. **Misperceptions about breast cancer treatment and its outcomes:** The interviewees noted the presence of community misunderstandings about breast cancer's causes, treatment, and prognosis. Amongst the patients and family members' interviewees, most had no response to the question, *"what do you think is the cause of breast cancer?"* However, some of the interviewees speculated based on their perspectives and the views in their communities. The speculated causes include sunstroke ("*Mitch"*), God as a penalty for their sins, evil eye, use of contraceptives, blunt trauma to their breast, failure to breastfeed, poor breast care, inheritance, and climate change. The most recurrently speculated cause of their illness was "*Mitch*". As some of the interviewees' conviction, they catch "Mitch" due to prolonged exposure to sunlight, especially during baking and preparing food at the open field (out of the home or shelter), and exposure to food odor during cooking thereby developed to their current breast illness.

"… Mine is caused by mitch because of excessive sun exposure. It happened when I took off my shirt during the hottest time of the day while working as a street vendor." (P02)

"… They (women with breast cancer) feel like they did sinful things to deserve such disease. Some patients relate the disease with the things they eat and drink or smoke…" (HP03)

A common view among respondents was that cancer is a severe, deadly, and incurable disease. As a result, a sense of desperation and fright of death from cancer was prevailing. These views surfaced mainly with the doubt these respondents had on the effectiveness of conventional treatment. Such views were particularly prominent in those who were considered aware of cancer and those who had a bad experience.

"How am I going to forget about the disease? I am carrying it … I think that I am going to die… other women also think that the disease cannot be cured and the person who has it is just waiting to die." (P09)

"…I told you that people think cancer as a fatal disease …That was how my mom felt. She tried to give us everything and did not even think about herself at all. She perceives as she does not have a life after the incident." (R03)

"… Some patients give up and refused to take the treatment. They preferred to go to traditional places/ holy water…" (HP05)

4. **Non-medical management of breast cancer symptoms:** Performing spiritual acts, such as using holy water, or seeking care from traditional healers was common amongst the women with breast cancer and family members interviewed. For most of the cases, the first action to the first symptoms was using traditional medicines. Medical consultation was often only then considered if the women/family member recognized these remedies are unsuccessful. Even after they visited health care, some of the women disregard the medical advice received, and return home to use different traditional medicines.

   "… I went to a traditional healer and he provided me an ointment, which I used for about 4 months. Then there was no change with the swelling… I waited for more than a year without visiting the health facility …" (P12)

   "… Some people completely healed by holy water… While I was in the hospital, one of my relatives advised me not to get breast surgery and rather to go to a traditional healer (Name). But I refused her advice …" (P06)

   "… There is traditional medicine even in Addis Ababa (capital city). … They insert something to the affected breast using a syringe. They say that the medicine will get rid of cancer from the breast …" (P02)

5. **Fear of cancer diagnosis:** Though issues related to fear of diagnosis were not particularly prominent in the interviewees, a few mentioned dreading the confirmation of their diagnosis. This fear was mainly ascribed to what the participants had heard in the community about the

severity of cancer. A common view among interviewees was that the word cancer is dreaded as incurable and fatal in their community. As a result, it is difficult to talk about cancer. Almost all of the patients and family members revealed that diagnosis of breast cancer was awful and scaring news for the clients and their families. This difficulty was due to low suspicion of breast symptoms as a sign of cancer, perceived seriousness of cancer, uncertainty about the effectiveness of conventional treatments, and fear of changes in body image after surgical removal of breast cancer.

"I do not know. When I recognized my first symptoms, I thought I will die of the disease immediately if it turns out to be cancer. I was afraid of going to the health facility … I lost my hope because, in the community, cancer is known as an incurable disease. It is called a killer." (P02)

"Oh, my God, I felt many things; having a breast removal at old age ... I had no pain at all. I felt why I have to go through breast removal at this age. I should die and get buried with dignity. I felt very sad." (P13)

"… They say that it is shameful if someone hears about it … A person should die with full body parts, but part of the body will be lost due to breast removal." (R03)

6. **Competing priorities:** The women interviewees responded that family responsibilities, such as looking after children and the inability to take time off from work, were their reasons to pay little attention to their first symptoms, usually a painless lump in the breast.

"… We have children who should go to school; we need to prepare food… We have a lot of work… You cannot leave them and run to the health facility." (P05)

7. **Financial insecurity:** The cost of transportation, investigation, and treatment was also mentioned as a reason for late diagnosis. Some of the patients reported returning home after being referred to a higher health facility for financial reasons, while others reported selling their property or borrowing money to get medical care.

"… I went to the health center. They told me to go to the hospital, but I did not have money to go to the hospital. Instead, I went to my home and stayed for months." (P01)

"… We had no money. We were forced to sell our cattle and our crops to cover the medical cost…" (P05)

"... I thought the cost of diagnosis was cheap, but it cost me 7500 birrs … I borrowed money from different sources as I did not want to see my wife die." (R01)

8. **Health system-related barriers:** Health professionals' misunderstanding of the first symptoms (telling women not to worry about their symptoms), inappropriate reassurance as

the lump is benign without taking a biopsy, long waiting times to receive diagnostic confirmation, few diagnostic centers, patient load, poor provider-patient communication and counseling were all mentioned as reasons for late diagnosis of breast cancer.

"… I noticed something a small lump on my breast... I woke up in the morning and went to my doctor. He told me it could be a tumor. I asked him if it could be cancer because I heard about it on TV. He told me it is not cancer." (P07)

"… Some of the attendants attempt to see the physicians even before the patients do. This is because there are patients who do not know that they have the disease thus the attendants try to talk to the physician in private/without the patient. There are attendants who suggest keeping the diagnosis in secret/ without the patient's awareness." (HP01)

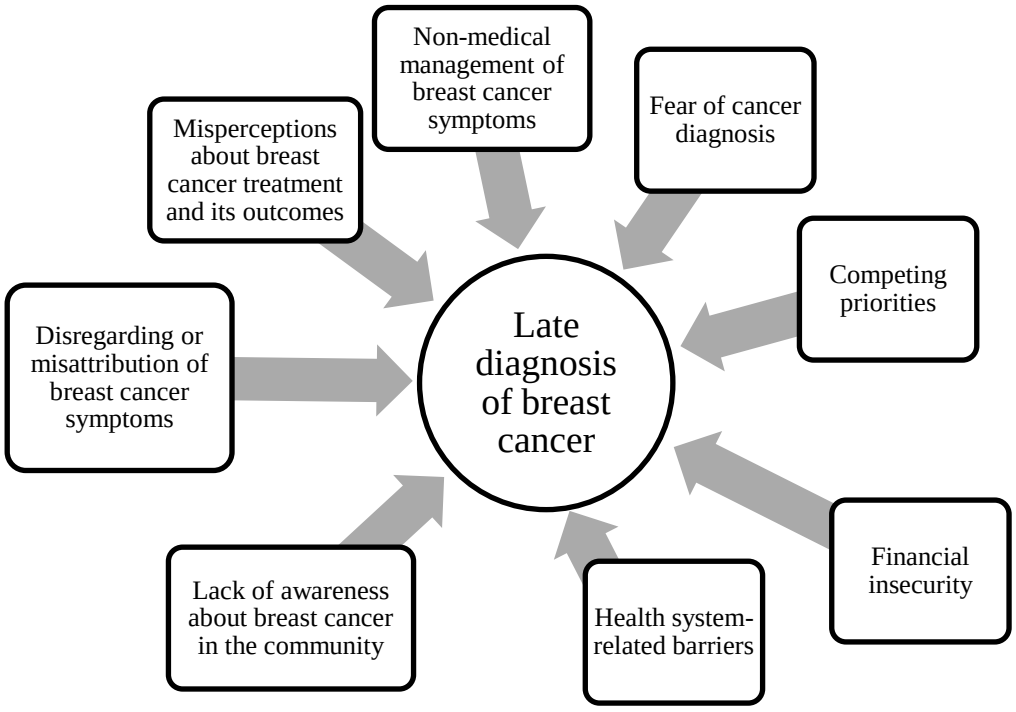

Figure 9: Summary of the reasons for late diagnosis of breast cancer, Oncology Clinic, TASH, Addis Ababa, Ethiopia, 2017

4.2.3. Facilitators of early diagnosis of breast cancer

In addition to the barriers, participants also pointed out the potential facilitators and the way forwards to improve the early stage diagnosis of breast cancer. Persuasion by family members and friends, prior experience of someone with breast cancer, and increasing the literacy level of the women were noted as the facilitators of early stage diagnosis. Family members and friends had a positive impact on the decision of patients to seek medical care, and knowing

someone who was treated for breast cancer was reported to be a facilitator of early medical consultations. Interviewees felt that women at a younger age with higher literacy levels were more likely to be early health care seekers in contrast to older or illiterate women. This view expressed mainly to emphasize the role of education on women's interpretation of the first symptoms of breast cancer and the decision to seek medical care.

"*… The influence of my friend working in the hospital made me seek medical care ... Had she did not push me, I would not have sought medical care. …" (P06)*

"*… I know a mother who was treated for breast cancer. When I felt the lump in my breast, I was shocked and immediately went to the hospital …" (P04)*

"*Younger women are better in seeking care. Older women did know nothing…" (P08)*

"*Those who are educated are more likely to seek care earlier… It is due to lack of knowledge…" (P05)*

4.2.4. Participants' suggestions to mitigate late diagnosis

In all cases, the informants suggested public health campaigns and programs enhance awareness about breast cancer symptoms, signs, and benefits of early identification and treatment to mitigate the late diagnosis of breast cancer. Involving breast cancer survivors in breast health education as community educators was also suggested.

"… We should use breast cancer survivors to educate the community that cancer can be cured if patients seek medical care as soon as they noticed the symptoms… I can teach the community about what I experienced with breast cancer. I do not think anyone of the breast cancer survivors will disagree to educate the community and save the lives of other women." (P03)

The participants emphasized the importance of regular breast self-examination and seeking medical attention following recognition of abnormal breast symptoms. The participants also suggested that interventions by the healthcare system to establish and expand counseling services, to reduce waiting times for diagnosis and treatment (expand diagnostic and treatment centers), and to mitigate the financial burden of cancer in patients and family members.

"… The burden of the disease is increasing; most of the services, however, are given in Tikur Anbessa Specialized Hospital only. Therefore, the government should open more facilities providing such services and strengthen the follow-up of patients." (P06)

4.3. Magnitude of advanced stage diagnosis and factors associated with advanced stage diagnosis of breast cancer

4.3.1. The magnitude of advanced-stage at diagnosis of breast cancer

Of these 441 women with breast cancer, in this analysis, we excluded women with unknown stage at diagnosis according to the American Joint Committee on Cancer stage (n=31) and those whose stage was only documented after neoadjuvant treatment (n=4). We analyzed the data of the remaining 406 women. The magnitude of stages I, II, III and IV at diagnosis was 13.1% (n=19), 31.0% (n=126), 44.6% (n=181) and 19.7% (n=80). Two-thirds of the women (64.3%, 95% CI [59.5%, 68.8%]) were diagnosed at advanced-stages (III and IV) of the disease. Nearly one third (30.6%) of the 64.3% were diagnosed after their disease had distant metastases primarily to liver, lung and bone. Taking the largest dimension of the tumor, the median tumor size at presentation was 4 (IQR: 3 to 6) centimeters.

The most common histologic type of tumor was ductal carcinoma (83.7%). Hormone receptor status was rarely determined. Among the 48 patients with known hormone receptor status, 33 (68.8%) were hormone receptor-positive (ER-and/or PR-positive), ten patients had triple-negative breast tumor. The histologic grade of one-fifth of the women's tumor was poorly differentiated (Table 9).

The median number of lymph nodes identified after surgical resection was 7 (IQR: 5 to 11). Only a third of the women (32.9%) with lymph node examination had a report of $\geq$ 10 lymph nodes identified. Among patients who had $\geq$ 10 lymph nodes examined, 26 (34.0%) were diagnosed with pN3. The rest 25 (32.0%) and 18 (23.0%) were diagnosed with pN1 and pN2, respectively. Thirty-five percent of the patients were in the high-risk lymph node ratio group (LNR >0.65) (Table 9).

Table 9: Clinical characteristics of women diagnosed for breast cancer from 1 January 2017- 30 June 2018 in Addis Ababa city, Ethiopia (n=406)

Characteristics	Frequency	Percentage
Tumor size at presentation (in greatest dimension)		
≤2 centimeters	44	10.8
>2-5 centimeters	165	40.6
>5 centimeters	100	24.6
Unspecified	97	23.9
Histological tumor type		
Ductal	340	83.7
Lobular	13	3.2
Mixed	16	4.0
Others	36	8.9
Unspecified	1	0.2
Hormone receptor status specified (n=48)		
Estrogen and progesterone positive	20	41.7
Estrogen positive and progesterone negative	9	18.7
Progesterone positive and estrogen negative	4	8.3
Estrogen and progesterone negative	15	31.3
Human epidermal growth factor 2 status (n=35)		
Positive	8	22.9
Negative	26	74.3
Equivocal	1	2.8
Histological grade		
Well-differentiated (Grade 1)	52	12.8
Moderately-differentiated (Grade 2)	123	30.3
Poorly-differentiated (Grade 3)	82	20.2
Unspecified	149	36.7
Surgical margin status (n=308)*		
Negative	205	66.6
Positive	48	15.6
Unspecified	55	17.8
Lympho-vascular invasion (n=308)[a]		
Negative	27	8.8
Positive	30	9.7
Unspecified	251	81.5
Pathologic tumor category (n=308)[a]		
T1	33	10.7
T2	133	43.2
T3	67	21.8
T4	46	14.9
Unspecified or unclear	29	9.4

Continued…

Table 9. Continued.

Characteristics	Frequency	Percentage
Number of lymph nodes examined (n=234)[b]		
1-9	157	67.1
≥10	77	32.9
Pathologic lymph node category (n=234)[b]		
PNx	51	21.8
pN0	8	3.4
pN1 (1-3)	25	10.7
pN2 (4-9)	18	7.7
pN3 (≥10)	26	11.1
N+ (Lymph node positive)	106	45.3
Lymph node ratio (n=234)[b]		
Low risk (≤0.20)	93	39.7
Intermediate risk (0.21-0.65)	60	25.6
High risk (>0.65)	81	34.7

pN: pathological lymph node category; [a]Results shown only for patients who had documented primary surgical management; [b]Results shown only for patients who had documented primary surgical management and number of LNs examined in the pathology report or medical chart

4.3.2. Factors associated with advanced-stage at diagnosis of breast cancer

In the multivariable analysis, the prevalence of advanced-stage at diagnosis was significantly higher among women who used traditional medicine before diagnosis (aPR=1.29, 95% CI [1.10, 1.52]). In contrast, the prevalence of advanced-stage at diagnosis was lower among women who practiced breast self-examination before symptom recognition (51.1%) compared to those who did not (67.9%) (aPR=0.77, 95% CI [0.63, 0.96]) (Table 10).

In the adjusted model, both patient delay of >3 months (aPR=1.16, 95% CI [1.00, 1.34]) and diagnosis delay of >2 months (aPR=1.24, 95% CI [1.07, 1.43]) were significantly associated with higher prevalence of advanced-stage at diagnosis (Table 10).

Table 10: Factors associated with advanced-stage at diagnosis among women with breast cancer diagnosed from 1 January 2017–30 June 2018, Addis Ababa city, Ethiopia (n=406)

Patient characteristics	Advanced-stage		Unadjusted		Adjusted
	No (%)	Yes (%)	PR (95% CI)	P-value	aPR (95% CI)
Age at diagnosis					NI
< 40	64(36.8)	110(63.2)	Ref.		
40 – 59	58(34.1)	112(65.9)	1.04(0.89, 1.22)	0.606	
≥ 60	23(37.1)	39(62.9)	0.99(0.79, 1.24)	0.965	
Women's education					NI
Not attended school	28(34.6)	53(65.4)	1.08(0.85, 1.35)	0.521	
Primary school	36(35.0)	67(65.0)	1.07(0.86, 1.33)	0.534	
Secondary school	46(34.6)	87(65.4)	1.07(0.87, 1.32)	0.479	
Diploma and above	35(39.3)	54(60.7)	Ref.		
Marital status					
Married	89(37.9)	146(62.1)	0.92(0.79, 1.06)	0.283	NI
Single, widowed or divorced	56(32.7)	115(67.3)	Ref.		
Had outdoor job					NI
No	75(33.3)	150(66.7)	Ref.		
Yes	70(38.7)	111(61.3)	0.92(0.79, 1.07)	0.270	
Family monthly income					
<61.0 $	38(31.2)	84(68.8)	1.15(0.94, 1.41)	0.172	1.05(0.85, 1.30)
61.0 - 194.0 $	68(36.4)	119(63.6)	1.06(0.87, 1.29)	0.534	1.00(0.83, 1.22)
>194.0 $	39(40.2)	58(59.8)	Ref.		Ref.
Source of medical expenses					NI
Out of pocket	104(36.2)	183(63.8)	0.91(0.67, 1.23)	0.542	
Free medical care	35(33.3)	64(64.7)	0.92(0.67, 1.27)	0.628	
Health insurance	6(30.0)	14(70.0)	Ref.		
Practiced BSE[a]					
No	102(32.1)	216(67.9)	Ref.		Ref.
Yes	43(48.9)	45(51.1)	0.75(0.60, 0.93)	0.011	0.77(0.63, 0.96)*
Breast pain as first symptom					NI
No	132(36.2)	233(63.8)	Ref.		
Yes	13(31.7)	28(68.3)	1.07(0.86, 1.34)	0.552	
Painless lump as first symptom					
No	26(30.6)	59(69.4)	Ref.		
Yes	119(37.1)	202(62.9)	0.90(0.77, 1.07)	0.242	0.87(0.74, 1.02)

Continued…

Table 10. Continued.

Patient characteristics	Advanced-stage		Unadjusted		Adjusted
	No (%)	Yes (%)	PR (95% CI)	P-value	aPR (95% CI)
Traditional medicine use[b]					
No	77(46.9)	87(53.1)	Ref.		Ref.
Yes	68(28.1)	174(71.9)	1.35(1.15, 1.59)	0.000	1.29(1.10, 1.52)***
Patient delay (>3 months)					
No	106(39.9)	160(60.1)	Ref.		Ref.
Yes	39(27.9)	101(72.1)	1.19(1.04, 1.38)	0.012	1.16(1.00, 1.34)*
Diagnosis delay (>2 months)					
No	80(43.5)	104(56.5)	Ref.		Ref.
Yes	65(29.3)	157(70.7)	1.25(1.07, 1.45)	0.004	1.24(1.07, 1.43)**
First medical consultation					
Public health center	51(35.2)	94(64.8)	1.06(0.89, 1.26)	0.468	0.96(0.80, 1.16)
Public hospital	29(30.5)	66(69.5)	1.14(0.95, 1.37)	0.151	1.05(0.88, 1.26)
Private hospital/clinic	65(39.2)	101(60.8)	Ref.		Ref.
# Health facilities visited[b]					NI
≤3	112(36.5)	195(63.5)	Ref.		
≥4	33(33.3)	66(66.7)	1.05(0.89, 1.23)	0.561	

$US dollar; [a]before symptom recognition; [b]before diagnostic; aPR: Adjusted Prevalence Ratio; BSE: Breast Self-Examination; NI: Not included in the multivariable model; #: number; *p < 0.05, **p<0.01, ***P < 0.001.

When we rerun the multivariable model replacing the patient and diagnosis delay by symptom interval (the sum of the patient and diagnosis interval), delay of >6 months in diagnostic confirmation following first symptom(s) recognition was significantly associated with higher prevalence of advanced-stage diagnosis compared to those who received diagnostic confirmation within 3 months from date of first symptoms recognition (71.2% vs 51.6%, aPR=1.35, 95% CI [1.12, 1.63]) (Table 11). In a sensitivity analysis, exclusion of patients who did not remember the day or month of first symptom recognition did not alter the findings on the association between delays and advanced-stage at diagnosis.

Table 11: The association between symptom interval and advanced-stage at diagnosis among women with breast cancer diagnosed from 1 January 2017–30 June 2018, Addis Ababa city, Ethiopia (n=406)

Symptom interval	Advanced-stage at diagnosis		Unadjusted		Adjusted*	
	No (%)	Yes (%)	PR (95% CI)	P-value	aPR (95% CI)	P-value
< 3 months	62(48.4)	66(51.6)	Ref.		Ref.	
3 – 6 months	26(35.1)	48(64.9)	1.26(0.99, 1.59)	0.058	1.23(0.97, 1.56)	0.075
> 6 months	57(27.9)	147(72.1)	1.40(1.15, 1.68)	0.001	1.35(1.12, 1.63)	0.002

*adjusted to the variables in table 10 (family monthly income, BSE, lump as first symptom, traditional medicine use, type of facility first medical consultation, and number of health facilities visited before diagnosis)

4.4. Survival rate of women with BC and its associations with delay and stage at diagnosis

4.4.1. Treatment pattern

Of the 441 women with breast cancer enrolled in the follow-up study, two were lost to follow-up and had no treatment-related data. Table 12 describes the treatment status of the 439 study participants. Seventy-nine percent of the women received surgical treatment predominately mastectomy.

Eighty-five percent (n=374) of the women received chemotherapy treatment. The median number of chemotherapy cycles received was 8 (IQR: 6 to 8). The median time to initiation of adjuvant chemotherapy was 63 days (IQR: 38 to 104), with 30.4% (95% CI [24.4%, 36.6%]) of women experiencing delay of >90 days (Table 12).

Less than a third (n=137, 31.2%) of the women had received radiotherapy, 64.2% (n=88) of which was adjuvant radiation. The median waiting time to initiation of adjuvant radiotherapy was 123 (IQR: 46 to 194) days, with 56.1% of the women experiencing delay of >90 days (Table 12).

Seventy-four percent of the women received hormonal therapy; specifically, tamoxifen (64%), anastrozole (23.8%), or letrozole (3.1%) (Table 12). Seventeen percent (n=44, 16.5%) of the women missed their regular hormonal therapy due to forgetting to take (41.0%), lack of drug (34%) and side effects (14.0%). Among those missed, 91.0% of them were for less than a month.

Table 12: Treatment status of women diagnosed with breast cancer from 1 January 2017 - 30 June 2018 in Addis Ababa city, Ethiopia (n=439)

Characteristics	Frequency	Percentage
Surgical therapy done (n=439)		
Yes	348	79.3
No	75	17.1
Unspecified	16	3.6
Type of surgery done (n=348)		
Mastectomy	320	92.0
Lumpectomy	7	2.0
Unspecified	21	6.0
Chemotherapy received (n=439)		
Yes	374	85.2
No	45	10.3
Unspecified	20	4.5
Type of chemotherapy (n=374)		
Anthracycline based only (AC, FAC, FEC)	103	27.5
Anthracycline + taxane (AC-T/ EC-T)	227	60.7
Others*	13	3.5
Unspecified	31	8.3
Delay to initiation of adjuvant chemotherapy (n=223)		
≤ 30 days	42	18.8
31-60 days	65	29.2
61-90 days	48	21.5
>90 days	68	30.5
Radiotherapy received (n=439)		
Yes	137	31.2
No	277	63.1
Unspecified	25	5.7
Aim of the radiotherapy (n=137)		
Adjuvant	88	64.2
Palliative	33	24.1
Unspecified	16	11.7
Adjuvant radiotherapy waiting intervals (n=57)		
≤ 30 days	7	12.3
31-60 days	13	22.8
61-90 days	5	8.8
>90 days	32	56.1
Hormonal therapy received (n=439)		
Yes	325	74.0
No	88	20.0
Unspecified	26	6.0

*****Cyclophosphamide/methotrexate/fluorouracil, Docetaxel and cyclophosphamide, Taxol, Dacarbazine and Adriamycin

Nine of the women with breast cancer refused the standard treatment partly or entirely. Three refused all the standard therapies (surgery, chemotherapy, radiotherapy, and hormonal therapy),

four refused chemotherapy, radiation, and hormonal treatment, one refused breast surgery, and one refused radiotherapy.

Of the 353 women who responded to the question "*Since you were diagnosed with the disease, were you unable to receive any form of treatments*?" 47(13.3%) experienced challenges of receiving the intended standard treatment. The main problems were lack of trust in the conventional treatment (34.4%, n=16), inability to afford the prescribed medications (29.8%, n=14), do not know where to go for treatment (12.8%, n=6), long waiting to get the treatment (8.5%, n=4), and absence of the treatment (4.2%, n=2). They also mentioned encountering challenges including fear of exposure of the diagnosis to family members (4.2%, n=2), fear of mastectomy (4.2%, n=2), considering the disease as self-healing, believing in holy water, and failure to obtain permission for work absence.

Eleven percent of the women used traditional medicine after diagnosis of their disease from herbalists or spiritual healers. The main reason for using traditional medicine was to treat their illness (75.0%, n=30). Other purposes mentioned include reducing the side effects of cancer treatment, relieving symptoms of their disease, being unaware of the standard cancer treatment, and lacking money for the standard treatment.

4.4.2. Two-year overall survival rate of women with breast cancer

The median follow-up time, calculated from the date of diagnosis, was 25.1 months (IQR: 19.3 to 31.4). By the end of the follow-up, 128 women died, making the cumulative incidence of death 29.2% (95% CI [25.0%, 33.6%]). Forty-percent (n=51) of the deaths happened within one year of diagnosis. The overall mortality rate over the 864.5 person-years follow-up was 148.0 deaths per 1000 person-years (95% CI [124.0, 176.0]).

Figure 10 shows the overall survival rate computed from date of diagnosis to the end of the follow-up. The overall one- and two-year survival rate was 88.3% (95% CI [84.9%, 91.0%]) and 75.2% (95% CI [70.7%, 79.0%]), respectively.

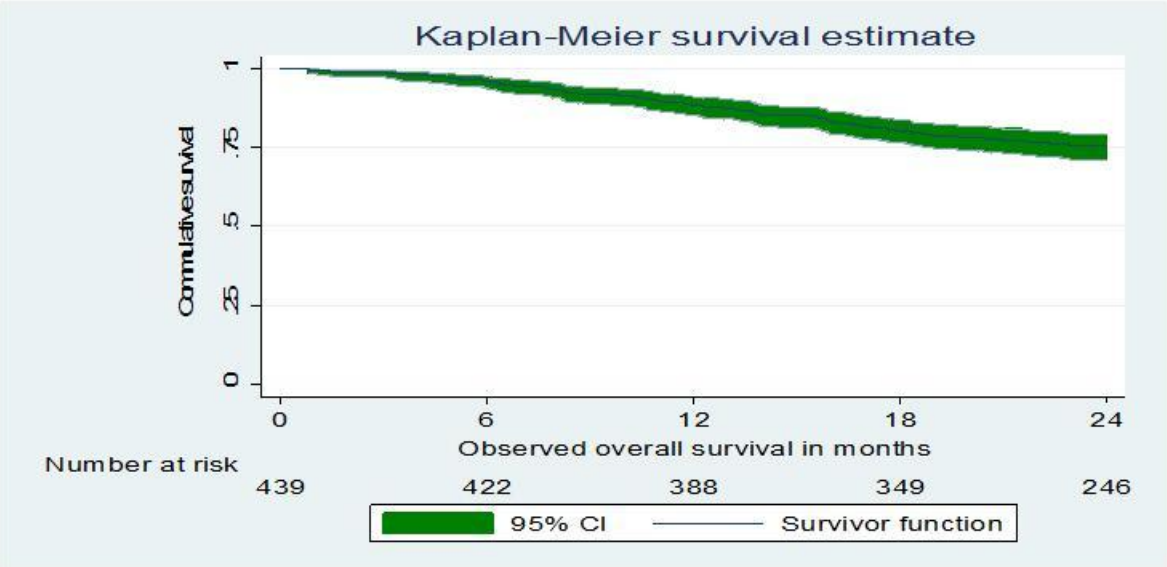

Figure 10: Overall survival rate of women with breast cancer diagnosed from 1 January 2017-30 June 2018 in Addis Ababa city, Ethiopia (Survival computed from date of diagnosis)

When the survival rate is computed from the date of first symptom recognition to the end of the study, the median follow-up was 33.8 months (IQR: 25.8 to 40.2). Over the 1411.6 person-years follow-up, the rate of death was 90.7/1000 person-years (95% CI [76.2, 107.8]). The one- and two-year overall survival rates were 96.3% (95% CI [94.0%, 97.7%]) and 85.0% (95% CI [81.3%, 88.1%]), respectively (Figure 11).

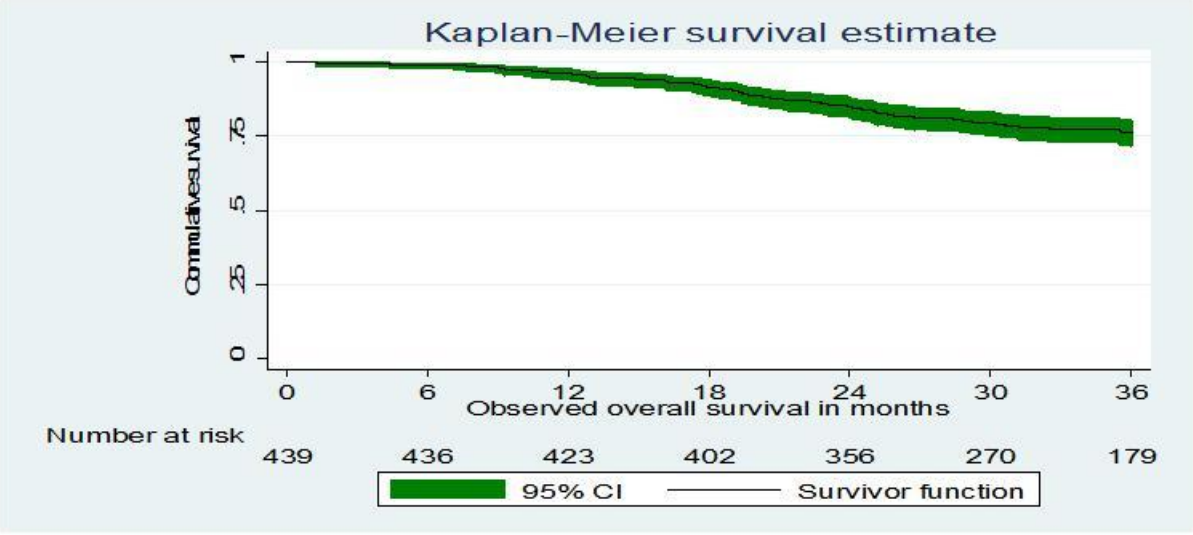

Figure 11: Overall survival rate of women with breast cancer diagnosed from 1 January 2017-30 June 2018 in Addis Ababa city, Ethiopia. (Survival computed from date of first symptom recognition)

One-fourth (n=112) of the women had documented comorbidities during diagnosis. The commonly reported comorbidities were hypertension (41.1%, n=46), diabetes mellitus (22.3%, n=25), HIV (17.8%, n=20), asthma (12.5%, n=14), cardiovascular diseases (11.6%, n=13),

kidney diseases (3.6%, n=4), and tuberculosis (3.6%, n=4). During the follow-up period, of the 308 cases with stage I-III and treated surgically, 31(10.0%) and 26(8.4%) had documented recurrence after surgery and metastasis after treatment initiation, respectively.

4.4.3. Determinants of overall survival of women with breast cancer

The overall survival rate was significantly lower among women diagnosed with advanced-stage (Figure 12) than those diagnosed with early stage of breast cancer. The one- and two-year overall survival rate of women diagnosed at stage I was 100%, while for stage IV was 62.0% and 26.7%, respectively (Table 13).

Table 13. Overall one- and two-year survival rate of women with breast cancer by stage at diagnosis in Addis Ababa city, Ethiopia

Stage at diagnosis	One year overall survival rate (95% CI)	Two year overall survival rate (95% CI)
Stage I	100.0%	100.0%
Stage II	96.0% (90.7%, 98.3%)	90.9% (84.2%, 94.9%)
Stage III	92.7% (87.9%, 95.7%)	80.8% (74.3%, 85.9%)
Stage IV	62.0% (50.4%, 71.7%)	26.7% (16.8%, 37.6%)

In the multivariable analysis, stage at diagnosis was the strongest predictor of women's 2-year overall survival. Women diagnosed at advanced-stage had about 3 fold increased risk of death (Adjusted hazard ratio ([aHR]) = 3.32, 95% CI [1.81, 6.10]) compared to those diagnosed at early stage (Table 14).

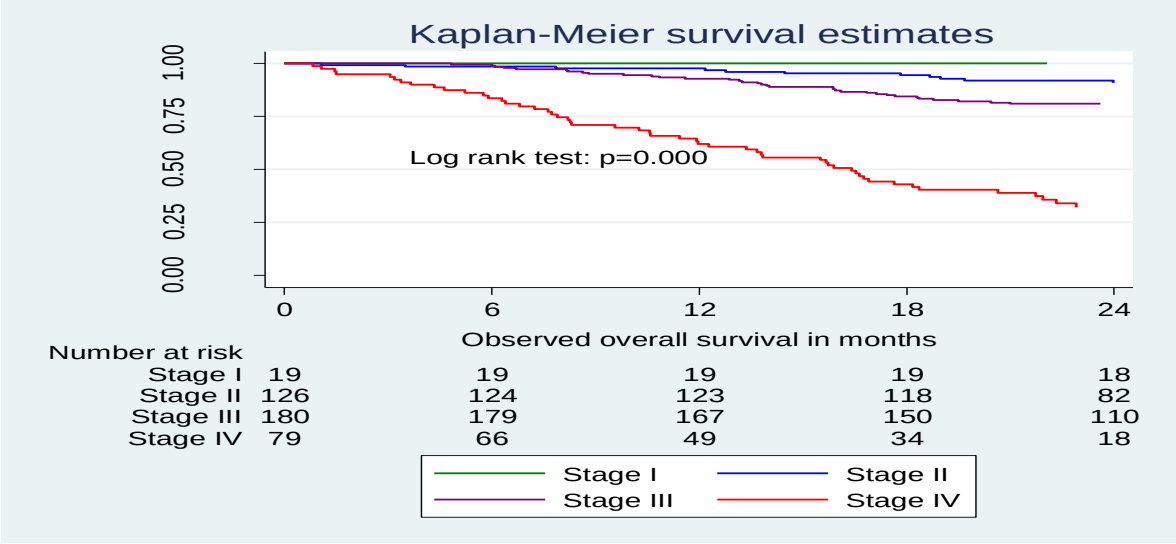

Figure 12: Overall survival rate of women with breast cancer diagnosed from 1 January 2017-30 June 2018 by stage at diagnosis in Addis Ababa city, Ethiopia

In addition to the stage at diagnosis, overall survival was lower among women who had symptom intervals of >3 months (Figure 13). After adjusting for stage at diagnosis and other variables in Table 14, delayed diagnosis following symptom recognition was significantly associated with increased risk of death. Women who delayed for >3 months before diagnosis (aHR=1.87, 95% CI [1.15, 3.03]) had 87% higher risk of death compared to these diagnosed within 3 months of symptom recognition (Table 14).

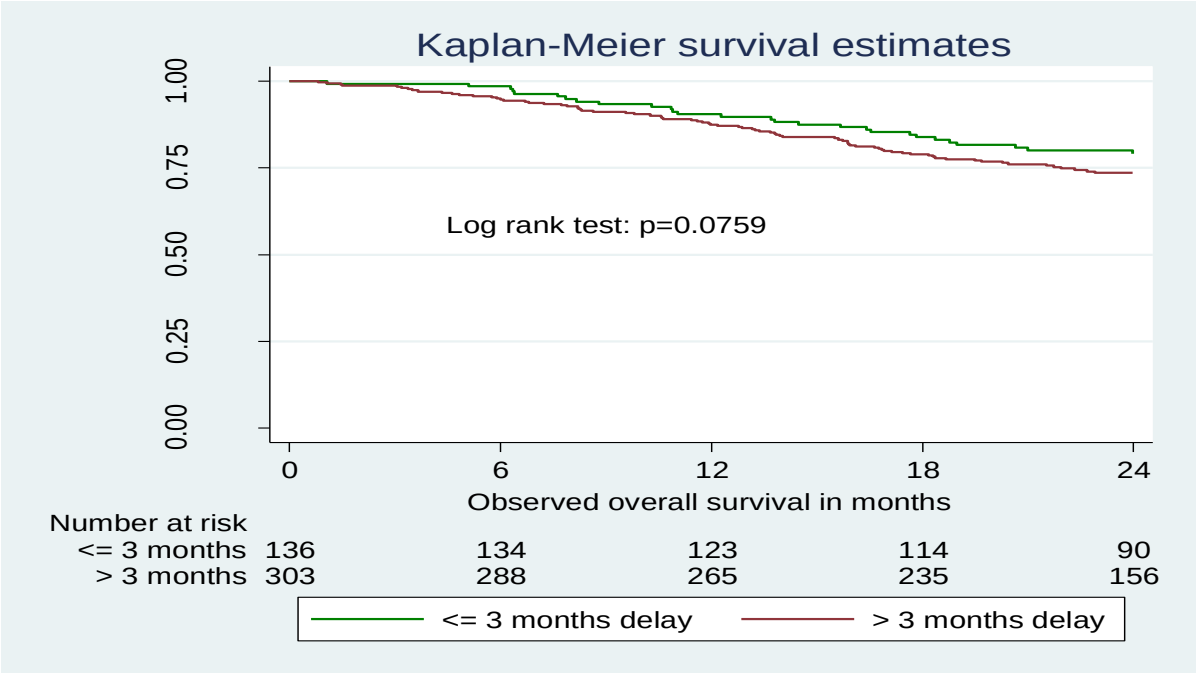

Figure 13: Overall survival rate of women with breast cancer diagnosed from 1 January 2017-30 June 2018 by symptom interval in Addis Ababa city, Ethiopia.

After controlling to stage at diagnosis and other variables in table 14, having surgical therapy (aHR=0.23, 95% CI [0.15, 0.35]) and hormonal therapy (aHR=0.26, 95% CI [0.17, 0.40]) had a protective effect on survival of women with breast cancer (Table 14).

Before adjustment, age at diagnosis of ≥60 years (HR=1.84, 95% CI [1.13, 2.99]) was significantly associated with increased risk of death. The association was, however, attenuated after adjusted to other variables in the model. Similarly, other socio-demographic variables: being unmarried at the time of diagnosis (HR=1.43, 95% CI [1.01, 2.03]), and having lower family monthly income (HR=1.68, 95% CI [1.04, 2.71]) were significantly associated with increased risk of death. Conversely, the risk of death was significantly lower among women having a diploma and above education (HR=0.43, 95% CI [0.24, 0.75]) than those who did not attend school. These associations were also attenuated after adjustment.

Partner education was negatively associated with death of women with breast cancer. Women with partner educational level of secondary school (HR=0.46, 95% CI [0.22, 0.97]) or diploma and above (HR=0.29, 95% CI [0.13, 0.63]) were at lower risk of death compared to those whose partner did not attend formal school. But, to keep our model's power, we did not include partner education into the multivariable model (Table 14).

Though the significant association was attenuated in the multivariable analysis, on bivariate analysis, the risk of death was higher among women who ever used traditional medicine before diagnosis (HR=1.89, 95% CI [1.28, 2.80]), and women with grad 3 (poorly differentiated) tumors (HR=2.19, 95% CI [1.03, 4.67]), and women having hemoglobin level of <12 g/dl at diagnosis (HR=1.96, 95% CI [1.19, 3.23]) but lower among women who had practiced breast self-examination before symptom recognition (HR=0.44, 95% CI [0.26, 0.74]) (Table 14).

Table 14: Cox regression analysis of determinants of overall survival of women with breast cancer diagnosed from 1 January 2017 - 30 June 2018 in Addis Ababa city, Ethiopia

Variables	Status at last contact		Bivariate Cox regression		Multivariable Cox regression
	Censored (%)	Death (%)	HR (95% CI)	P-value	aHR (95% CI)
Age at diagnosis (years)					
<40	138(75.8)	44(24.2)	Ref.		Ref.
40-59	129(69.0)	58(31.0)	1.33(0.90, 1.97)	0.146	1.34(0.83, 2.16)
≥60	42(61.8)	26(38.2)	1.84(1.13, 2.99)	0.014	1.18(0.61, 2.25)
Participants' education					
Not attended school	53(61.6)	33(38.4)	Ref.		Ref.
Primary school	78(69.6)	34(30.4)	0.76(0.47, 1.23)	0.266	1.12(0.62, 2.01)
Secondary school	100 (71.4)	41(29.3)	0.67(0.42, 1.06)	0.086	0.94(0.52, 1.72)
Diploma and above	79(79.8)	20(20.2)	0.43(0.24, 0.75)	0.003	0.84(0.38, 1.87)
Partner's education					
Not attended school	14(56.0)	11(44.0)	Ref.		Not included[c]
Primary school	40(67.8)	19(32.2)	0.64(0.30, 1.36)	0.247	
Secondary school	63(75.9)	20(24.1)	0.46(0.22, 0.97)	0.043	
Diploma and above	74(83.2)	15(16.8)	0.29(0.13, 0.63)	0.002	
Marital status					
Married	189(74.4)	65(25.6)	Ref.		Ref.
Single, widowed or divorced	120(65.6)	63(34.4)	1.43(1.01, 2.03)	0.042	1.25(0.82, 1.90)
Had outdoor job					
No	158(66.7)	79(33.3)	Ref.		Ref.
Yes	151(75.5)	49(24.5)	0.70(0.49, 1.01)	0.058	1.01(0.62, 1.63)
Family monthly income					
<61.0 US$	89(68.5)	41(31.5)	1.57(0.94, 2.62)	0.082	0.74(0.39, 1.40)
61.0-194.0 US$	135(67.8)	64(32.2)	1.68(1.04, 2.71)	0.032	1.44(0.84, 2.49)
>194.0 US$	85(78.7)	23(21.3)	Ref.		Ref.
Practiced BSE[a]					
No	228(67.3)	111(32.7)	Ref.		Ref.
Yes	81(82.6)	17(17.4)	0.44(0.26, 0.74)	0.002	0.59(0.32, 1.06)
Traditional medicine use before diagnosis					
No	140(80.0)	35(20.0)	Ref.		Ref.
Yes	169(64.5)	93(35.5)	1.89(1.28, 2.80)	0.001	0.86(0.49, 1.49)
Symptom interval					
≤3 months	103(75.7)	33(24.3)	Ref.		
>3 months	206(68.4)	95(31.6)	1.44(0.97, 2.14)	0.070	1.87(1.15, 3.03)*

Continued …

Table 14. Continued.

Variables	Status at last contact		Bivariate Cox regression		Multivariable Cox regression
	Censored (%)	Death (%)	HR (95% CI)	P-value	HR (95% CI)
Histologic tumor grade					
Grade 1	43(82.7)	9(17.3)	Ref.		Ref.
Grade 2	98(77.8)	28(22.2)	1.35(0.63, 2.87)	0.429	1.24(0.53, 2.89)
Grade 3	56(66.7)	28(33.3)	2.19(1.03, 4.67)	0.041	1.59(0.70, 3.69)
Not specified	112(64.0)	63(36.0)	2.29(1.14, 4.62)	0.020	1.51(0.68, 3.36)
Advanced-stage at diagnosis					
No	131(90.3)	14(9.7)	Ref.		Ref.
Yes	155 (59.8)	104(40.2)	5.02(2.87, 8.78)	0.000	3.32(1.81, 6.10)***
Not specified	23(69.7)	10(30.3)	3.57(1.58, 8.04)	0.002	1.23(0.32, 4.71)
Hemoglobin level during diagnosis					
<12.0 g/dl	22(53.7)	19(46.3)	1.96(1.19, 3.23)	0.008	1.09(0.61, 1.95)
≥12.0 g/dl	240(73.4)	87(26.6)	Ref.		Ref.
Not specified	47(68.1)	22(31.9)	1.18(0.74, 1.89)	0.477	0.52(0.26, 1.04)
Co-morbidities at diagnosis					
No	224(68.9)	101(31.0)	Ref.		Not included
Yes	85(75.9)	27(24.1)	0.81(0.51, 1.27)	0.357	
Surgery therapy					
No	21(28.0)	54(72.0)	Ref.		Ref.
Yes	284(82.3)	61(17.7)	0.16(0.11, 0.23)	0.000	0.23(0.15, 0.35)***
Delay to adjuvant chemotherapy					Not included
≤90 days	136(85.0)	24(15.0)	Ref.		
>90 days	62(84.9)	11(15.1)	0.90(0.44, 1.84)	0.783	
Radiotherapy					Not included
No	207(74.7)	70(25.3)	Ref.		
Yes	96(70.1)	41(29.9)	1.09(0.74, 1.60)	0.653	
Hormonal therapy					
No	40(46.0)	47(54.0)	Ref.		Ref.
Yes	262(80.9)	62(19.1)	0.24(0.17, 0.36)	0.000	0.26(0.17, 0.40)***

[a]before symptom recognition; BSE: Breast self-examination; $=US dollar; aHR=adjusted hazard ratio; [c]partner's education (n=256) is not included in the model since it decreases the power of the model; *p < 0.05, **p < 0.01, ***P < 0.001.

4.5. Summary of the main findings of the dissertation

Table 15 presents the summary of the key findings of the dissertation by specific objectives.

Table 15: Summary of the key findings of the dissertation by specific objectives, Addis Ababa, Ethiopia

Objectives	Major findings
To determine the magnitude of delays (patient and diagnostic), and factors associated with these delays of women with BC	• **Patient delay (>90 days)** ✓ Magnitude of patient delay: 35.7% (95% CI [31.1%, 40.3%]) ✓ Main causes: Not bothered by the problem at first, using holy water/visiting traditional healers first, and unable to take time off from work ✓ Factors associated: Using traditional medicine before consultation (aPR=2.13, 95% CI [1.68, 2.71]). • **Diagnosis delay (>30 days)** ✓ Magnitude of diagnosis delay: 69% (95% CI [64.6%, 73.3%]) ✓ Main causes: Misdiagnosis, false-negative laboratory results, lack of empathy at first medical consultation, use of traditional medicine, fear of cancer diagnosis and treatment, lack of awareness about disease severity, and financial difficulties for diagnosis and treatment ✓ Factors associated: ✓ First consultation at health centers (aPR=1.19, 95% CI [1.02, 1.39]) ✓ Visiting ≥4 facilities (aPR=1.24, 95% CI [1.10, 1.40]) ✓ Progression of symptoms before consultation (aPR=0.73, 95% CI [0.60, 0.90])
To explore the reasons for late diagnosis of women with BC	• **The main reasons for late diagnosis:** Lack of awareness about breast cancer in the community, ignoring of breast cancer symptoms, misperceptions about breast cancer treatment and its outcomes, non-medical management of breast cancer symptoms, fear of cancer diagnosis, competing priorities, financial insecurity, and health system-related barriers. • **The facilitators of early diagnosis:** Persuasion by family members and friends, prior experience of someone with breast cancer, and literacy level of the women • **Ways forward to improve early diagnosis:** Public health campaigns targeted at improving community awareness on breast cancer, involving breast cancer survivors as community educators, regular BSE, and cancer service expansion
To identify factors associated with advanced-stage at diagnosis of women with BC	• Magnitude of advanced-stage at diagnosis: 64.3% (95% CI [59.5%, 68.8%]), ✓ 30.7% (n=80) of these were with metastasized disease • Factors associated with advanced-stage at diagnosis: ✓ Ever practice of breast self-examination (aPR=0.77, 95% CI [0.63, 0.96]) ✓ Traditional medicine use before diagnosis (aPR=1.29, 95% CI [1.10, 1.52]) ✓ Patient delay of >3 months (aPR = 1.16, 95% CI [1.00, 1.34]) ✓ Diagnosis delay of >2 months (aPR=1.24, 95% CI [1.07, 1.43])
To determine two-year survival rate and its associations with delay and stage at diagnosis of women with BC	• Overall mortality rate over the 864.5 person-years follow-up was 148.0 deaths per 1000 person-years (95% CI [124.0, 176.0]) • Two years overall survival rate was 75.2% (95% CI [70.7%, 79.0%]) ✓ 100% among stage I versus 26.7% among stage IV • Main determinants of two years overall survival were: ✓ Advanced-stage at diagnosis (HR=3.32, 95% CI [1.81, 6.10]) ✓ Symptom interval >3 months (HR=1.87, 95% CI [1.15, 3.03]) ✓ Surgical treatment (HR=0.23, 95% CI [0.15, 0.35]) ✓ Hormonal therapy (HR= 0.26, 95% CI [0.17, 0.40])

5. Discussion

The study used a mixed method to understand the problem of delay diagnosis following symptom recognition of breast cancer from different perspectives and complement the findings. The magnitude of delays was quantified using the cross-sectional study design, and the reasons for late diagnosis were explored using the qualitative method. The qualitative results complemented the quantitative findings and helped to have a complete understanding of the problem. The mix could be done at a different stage of research [131]; in this case, the mix is done from this section onwards. Thus, the discussion section is systematically organized into the following subsections.

5.1. Time intervals experienced between first symptom recognition and treatment initiation

5.1.1. Magnitude of patient and diagnosis delays

The study found that women with breast cancer in Addis Ababa have experienced patient and diagnostic delays, with one-third of the patients waiting for >3 months before seeking medical care, and nearly two-thirds of the patients waited over a month before receiving diagnostic confirmation. Patient delay was significantly higher among women who used traditional medicine before consultation. Diagnostic delay was higher among women who first consulted at health centers and visited four or more health facilities before diagnosis but lower among women who experienced progression of symptoms before consultation.

In this study, the magnitude of patient delay was substantially lower than those found in two single institution-based studies in Addis Ababa [14, 29]. Our study's lower magnitude of patient delay can be explained in part by the differences in the study participants' residence and improvement in patients' awareness over the last 13 years (2003-2015) since the previous studies were conducted. About one-third of the patients in the single-institution based studies [14, 29] resided outside of Addis Ababa, and patients living outside the city have been reported to have less knowledge about breast cancer and less access to health care services [15].

Similarly, compared to studies in sub-Saharan African countries, the median patient interval in our study (30 days) was considerably shorter than those reported from Rwanda (150 days) [58] and Mali (144 days) [32], but comparable with that reported from South Africa (23 days) [147]. As expected, compared to findings from countries outside of sub-Saharan Africa, our finding of median patient interval is generally longer [73, 148].

Our finding of median diagnostic interval (69 days) was lower than that reported in Rwanda (150 days) [58] but longer than those reported in Mali (27 days) [32] and South Africa (28 days) [147]. Sixty-nine percent of the patients in our study waited for >30 days, and 18% for over a year to receive diagnostic confirmation following first medical consultation for their disease.

This study was conducted in the capital city, Addis Ababa, where the population has better access to health information and service than the rural part of Ethiopia [15]. However, substantial number of women with breast cancer in the city experienced patient and diagnostic delays due to both individual and health care provider related factors. The diagnosis delay is more common than patient delay. This may in part reflect lack of referrals to a specialized center for a substantial proportion of patients with suggestive signs and symptoms of breast cancer, which in turn calls for training of front-line health workers to improve their clinical suspicion skills and early referral. Moreover, strengthening the referral linkage between the health centers and hospitals could increase early detection of breast cancer.

5.1.2. The reasons for late diagnosis of breast cancer

The reasons for late diagnosis following symptom recognition found from the survey and qualitative findings complement each other. We found lack of awareness about breast cancer in the community, disregarding or misattribution of breast cancer symptoms, misperceptions about breast cancer treatment and its outcomes, non-medical management of breast cancer symptoms, fear of cancer diagnosis and treatment, competing priorities, financial insecurity, and health system-related barriers (misdiagnosis, long patient list to diagnosis, poor patient-physician communication and counseling) as the main reasons of late diagnosis.

Women's and community awareness on breast cancer risk factors, early detection methods, initial symptoms, and treatments are essential for encouraging women to seek medical care immediately after recognizing the first symptoms [149-150]. However, in this study, women's awareness of breast cancer before symptom recognition was uncommon, contributing to delayed consultation. A third of the women with breast cancer had never previously heard of breast cancer. Furthermore, it was hard for most women to think of cancer during recognition of the first symptom of their breast illness. Only 8.0% of women thought the first symptom was a symptom of breast cancer while the rest were attributed to other non-specific conditions. They misinterpreted as the symptom is related to non-cancer diseases, such as sunstroke, locally termed

“mitch.” In Ethiopia, “mitch” is a local and common terminology used to explain a wide range of nonspecific illnesses in the community [151]. Such beliefs triggered women to practice different home remedies, spiritual acts, and traditional medicines intended to treat the perceived cause of their illness, “mitch”. The misattribution of the symptoms is related to the women’s low perceived susceptibility to breast cancer and poor awareness of breast cancer's initial symptoms. In addition, the painless nature of the first breast cancer symptom, which is commonly breast lump, increased the tendency of disregarding first symptom's clinical importance. Women are commonly less likely to perceive the disease as severe and seldom seek medical care if they are not acutely sick [152]. Sharp and colleagues also noted that “knowledge deficit a modifiable factor” was the main barrier to early detection of breast cancer in Uganda [22].

Furthermore, family responsibilities and inability to take time off from work increased the risk of disregarding the severity of the first symptom(s). Previous studies [67, 153] have also noted that women’s family engagements and job commitment are contributor to delayed medical consultation. These findings imply that increasing awareness of signs and symptoms of breast cancer in the community could minimize such negligence and misattribution of breast cancer's first symptoms.

Studies in Ethiopia documented that many sick people prefer visiting traditional healers before seeking medical care [152, 154]. Birhan and colleagues [154] reported that cancer patients were among the most frequent visitors to traditional healers in Addis Ababa. Similarly, our study revealed that use of traditional medicine was common and the main cause of late diagnosis. Thirteen percent of our study participants’ immediate response to the first breast cancer symptoms was using traditional medicines. This practice was significantly associated with increased prevalence of patient delay. The finding from our qualitative study also revealed, for some breast cancer patients, seeking medical care was their second option, only after traditional medicine failed to provide hope of a cure. Previous studies in Ethiopia [14, 29] and other parts of Africa [32, 58, 155] documented that the time elapsed while using traditional medicine contributes to patient delay. The time elapsed while practicing traditional medicine and late recognition of the first symptoms could further advance the disease stage and complicate its treatment outcomes. The present study raises the possibility that involvement and working with traditional healers to create awareness about the symptoms of breast cancer and benefits of early referral for diagnosis could benefit the women who visited traditional healers for the complaint of

breast abnormality. Also, more research on traditional healers' views on breast cancer diagnosis and treatment needs to be undertaken.

Contrary to misinterpretations of the symptoms, some participants admitted suspecting cancer with their first symptoms but refrained from visiting a health facility fearing cancer diagnosis. This fear was mainly due to the community's view that cancer is a deadly disease and incurable with the existing conventional treatment in the country. Similar experiences were reported in other studies from Ethiopia [35, 156], India [150], and Iran [153]. Thus, educating the community about the benefits of early diagnosis and treatment initiation could help correct the misperceptions and improve women's health-seeking behavior with symptoms suggestive of breast cancer [157].

Health care provider related factors that may have contributed to the considerably prolonged diagnostic interval, as reported by the patients, include difficulties of navigating the healthcare system, and misdiagnosis of clinical manifestations. In the multivariable analysis, diagnostic delay was significantly associated with first consultation at a health center, and visits to $\geq$ 4 healthcare facilities before diagnosis. On average, patients visited at least three different healthcare facilities and made about seven visits before receiving diagnostic confirmation. The number of visits was substantially higher among those patients whose first consultation was at a health center, in part because of the additional time needed for referring patients to hospitals [129]. This may also reflect a low level of breast cancer knowledge among both providers and patients in the health centers, as health center providers are more likely to be low- or mid-level health professionals. Also, women visiting health centers are more likely to be less educated than those visiting private clinics or hospitals. A study conducted among female nurses [91] in Addis Ababa found poor general knowledge about breast cancer.

Our findings also suggest the presence of providers' oversight of initial breast cancer symptoms leading to delayed referral of the women with first symptom(s) for confirmation. In contrast, patients who sought medical consultation after progression of symptom(s) had lower prevalence ratio of diagnostic delay. This is likely because more extensive breast symptoms or signs may have led to prompt referral of patients to diagnostic centers, as reported elsewhere [107, 158].

The qualitative findings also provided a detailed explanation about health system-related factors contributing to late diagnosis. Health professionals' misunderstanding of the first symptoms,

inappropriate reassurance of lump as a benign disease without biopsy, and inadequate counseling of patients presenting with signs and symptoms suggestive of breast cancer, were noted as contributors to late diagnosis. These results agree with the findings of other studies, in which health care providers' failure to appraise the first symptoms of breast cancer appropriately and misdiagnosis contributed to delayed diagnosis and disease advancement [73, 159]. While preliminary, these quantitative and qualitative findings underscore the need for training primary health care providers [160-161] to recognize the first symptoms of breast cancer, and increase the suspicion of breast cancer at first contact. Moreover, breast cancer patients need appropriate advice and discussion on their problems, consequences, and treatment decisions.

Like other literature [159, 162-163], different patient-related factors were also noted as causes of the diagnosis delay. Some women tend to go back to traditional medicine even after they consulted for their illness or referred for diagnostic confirmation. Also, fear of cancer diagnosis and treatment leading patients to deny diagnostic procedures, such as fine needle aspirations or biopsy, perceiving that the manipulation could worsen or disseminate cancer and breast removal make the women disappear for a while or visit other health facilities for a second opinion. These factors contributed to the multiple health facility visits and diagnosis delay. Besides, time and financial barriers were also reported as influencing the diagnostic interval.

Some portion of the diagnosis delays we observed could be attributed to pathology result turnaround times in the few available diagnostic facilities in the city. Like other sub-Saharan African countries [164], cancer patients in Addis Ababa waited on average for fifteen days to get the pathology result [19].

In contrast to the above barriers, the persuasion by family members and friends was mentioned as a facilitator for patients to seek medical consultations after they recognized breast cancer symptoms and decide to diagnose and undergo surgical treatment. This finding was also documented in a previous study conducted in the city [29]. Thus, educating women and their significant others about the symptoms, screening methods, and breast cancer management could improve the women's health-seeking behavior, thereby shortening the diagnosis interval.

Early detection is the primary strategy for preventing premature death from breast cancer. Hence, interventions targeted at alleviating the above modifiable barriers [150] must be established in Ethiopia to diagnosis breast cancer at earlier stages. In settings, like Ethiopia, with limited breast

cancer screening services mainly in Addis Ababa or other parts of Ethiopia, early detection is largely dependent on woman's knowledge on breast cancer [36], performing regular BSE and immediate medical consultations after recognition of breast abnormalities [165-166], and health care providers' timely evaluation and referral for confirmation [167]. Our study participants also emphasized the importance of breast self-examination, early medical care-seeking, awareness creation, and cancer diagnostic center expansion to improve early detection. Moreover, the study participants emphasized the importance of using breast cancer survivors as community educators to enhance breast cancer awareness. Though this approach's effectiveness has not been investigated in our country, engaging breast cancer survivors as breast health educators [168-170] has led to significant improvement in the knowledge and early detection of breast cancer.

5.1.3. Treatment initiation and total delays

In addition to the patient and diagnostic delays, we systematically examined the extent of treatment initiation delay. Half of the women started first treatment within 29 days of diagnosis, and 98.6% of the women initiated the treatment within a year of diagnosis. Our cohort's treatment initiation interval is shorter than the treatment interval reported in other sub-Saharan African countries where 17% of the women with breast cancer had not initiated treatment within a year of diagnosis [171]. However, the treatment initiation interval was higher than reports from developed countries where half of the women initiated the treatment within two weeks of diagnosis [172].

Half of the women with breast cancer in Addis Ababa had initiated first treatment after seven months of symptom recognition. The median total interval was comparable with a finding from Mexico [101] and other low and middle-income countries, but significantly higher than the estimates made for high-income countries where the total median interval ranged from 30 to 40 days [57]. The sub-interval taking the highest share of the total interval was diagnosis interval (median = 69 days). This may, in part, reflect lack of referrals to a specialized center for a substantial proportion of patients with suggestive signs and symptoms of breast cancer, which, in turn, calls for training of front-line health workers to improve their clinical suspicion skills and early referral. Moreover, strengthening the referral linkage between the health centers and hospitals could increase early detection of breast cancer.

We also examined the time to initiation of adjuvant chemotherapy following surgery among women with stage I-III breast cancer in Addis Ababa. We found that nearly a third of women were delayed in initiation of adjuvant chemotherapy. The proportion of delay to initiation of adjuvant chemotherapy in Addis Ababa was substantially higher than those reported for women in developed countries [84, 173]. For example, Fedewa and colleagues [84] found that only 4.8% of women with breast cancer in the United States had not received adjuvant chemotherapy within 90 days of surgery. The higher rate of delay to initiation of adjuvant chemotherapy in Addis Ababa also in part reflect the limited number of cancer treatment centers and availability of drugs [19]. Because of lack of widespread public or private health insurance program in Ethiopia, a majority of patients pay their medical bill out of pocket. Those patients who cannot afford out of pocket payment receive treatment in government hospitals free of charge or heavily subsidized after procuring certificate from their jurisdiction. But the difficulty of affording drugs that are out of stock in the public pharmacies is the challenge for the women with lower socioeconomic status [174]. These findings underscore the need for public policy to expand access to health care to low-income population to improve breast cancer care and other health outcomes in the country.

5.2. Factors associated with advanced-stage diagnosis

The study found a high proportion of advanced-stage diagnoses. Sixty-four percent of the patients were diagnosed at advanced-stage of their disease, with 19.7% metastatic disease at initial presentation. Use of traditional medicine before diagnosis, patient delay of >3 months following date of recognition of breast symptom, and diagnosis delay of >2 months following date of medical consultation for breast symptom were significantly associated with increased prevalence of advanced-stage at diagnosis. In contrast, practicing breast self-examination before symptom recognition was associated with decreased prevalence of advanced-stage at diagnosis.

In our study, the magnitude of advanced-stage at diagnosis as expected was significantly lower than that found in the rural part of Ethiopia (85%) [33] and slightly higher than that seen in a study conducted in one private clinic in Addis Ababa (55%) [14]. The variation could be mainly due to the differences in the study participants' socio-economic status and access to health information and health facilities. Our estimate is comparable with the population-based data estimates made for sub-Saharan Africa (64.9%) [10] but as expected significantly higher than the findings from countries outside of sub-Saharan Africa: Iran (36.2%) [77] and USA (26.6%) [100].

The stage at diagnosis is an essential independent factor determining the choice of treatment, and survival rate [105] of women with breast cancer. Women diagnosed at advanced-stage usually receive palliative therapy and have poor prognosis than those diagnosed at their early stage [175]. In addition, late-stage tumor is more difficult and costly to treat compared with early-stage tumors [176]. The magnitude of advanced-stage at diagnosis is more prominent in sub-Saharan African countries [105], where there are a limited number of early detection services and treatment centers. Similar to other sub-Saharan African countries, in Ethiopia, advanced-stage at diagnosis of breast cancer is common, and associated with poor survival [13, 18, 32] and increased burden on the existing limited cancer treatment centers in the country [19, 177].

The proportion of women diagnosed with the advanced-stage disease is likely to be considerably higher in other parts of the country than that in Addis Ababa as health literacy level and access to health are inferior. For instance, Deressa and colleagues [33] found that 85% of women with breast cancer in Northern Ethiopia diagnosed at an advanced-stage. Thus, downstaging of breast cancer in Ethiopia and other resource-limited settings helps not only cancer patients and their families but also governments by decreasing costs associated with morbidity, premature mortality, and productivity loss.

Downstaging of breast cancer could be achieved through implementation of interventions to reduce known risk factors such as knowledge deficits [22], traditional medicine use [178], and being uninsured [179]. We found that traditional medicine use before diagnosis was significantly associated with advanced-stage at diagnosis. According to different studies, the prevalence of traditional medicine use in Ethiopia ranged from 61% to 71% [180-181]. Another study conducted in Addis Ababa, the capital city of Ethiopia, documented as cancer patients were among the most common visitors to traditional healers in the city [154]. People preferred to use traditional medicine because of dissatisfaction with the modern medicine, accessibility, affordability and acceptability of traditional medicine in the community [154, 180]. The other possible reason noted from the qualitative study was false belief that cancer can be cured with traditional medicine and to avoid treatment like mastectomy. The time elapsed while practicing traditional medicine is attributing to the advancement of the disease before diagnosis. Akhtar and colleagues reported that women in Bangladesh on average waited 3 months using traditional medicines before making medical consultation and there was a positive correlation between traditional medicine use and delayed diagnosis [178], which further increase the tendency of

progression of the disease and make the conventional treatments unsuccessful [182-183]. An implication of this is the possibility that involving traditional healers in breast health education to reduce diagnostic delay, promote early detection, and downstaging of the disease in Ethiopia and other economically developing countries.

Our findings of statistically significant higher prevalence of advanced-stage at diagnosis among women who had patient and diagnosis delays are consistent with previous reports [21, 77]. The association of diagnosis delay with advanced-stage at diagnosis was more overt than patient delay. As noted in the qualitative findings, reasons for delayed diagnosis include both provider and patient factors such as misdiagnosis, traditional medicine use, fear of diagnosis, and financial barriers. Therefore, interventions to improve patient and provider knowledge about breast cancer in the country may shorten delays in diagnostic confirmation thereby increase early stage diagnosis.

We found that women who had practiced breast self-examination before symptom recognition had lower prevalence of advanced-stage at diagnosis. Women who practiced breast self-examination are likely to be more aware of breast cancer and seek care earlier than their counterparts. Moreover, McKenzie et al. [21] also found significant association between lack of breast cancer awareness before symptom recognition and advanced-stage at diagnosis. These findings also concur with the results obtained in the qualitative study, where a lack of awareness about breast cancer symptoms and signs was commonly reported reasons for late diagnosis of the disease.

Our findings of the association between advanced-stage diagnosis and traditional medicine use before diagnostic confirmation, patient delay, and diagnosis delay, practice of breast self-examination before symptom recognition in Addis Ababa suggest that advanced-stage at diagnosis could be downstaged by enhancing breast cancer knowledge among women and practice of regular breast self-examination, and shortening the time intervals elapsed by the patients and health care providers. Downstaging could be achieved by increasing public awareness on breast health, and symptoms and signs of breast cancer. Women mentioned health care providers as it was the least source of breast cancer information before they recognized the first symptom(s) of breast cancer, only 5.7% of the cohort mentioned health care providers as their source of breast cancer information. From my personal observation, in the health centers and health posts, breast cancer or cancer related diseases were not in the list of health education

topics. Thus, inclusion of breast cancer in the health education topics while improving the front-line health workers' competencies, and attention to potential of breast cancer at first consultation and installment of diagnostic clinics could improve the timely diagnosis of breast cancer [160].

5.3. Survival rate of women with BC and its associations with delay and stage at diagnosis

This study determined the incidence of death and its determinants among women with breast cancer. The incidence rate of death was 148 deaths per 1000 person-years (95% CI [124.0, 176.0]). Three-fourths of the women with breast cancer were alive at two years of their diagnosis (75.2%; 95% CI [70.7%, 79.0%]). The hazard of death was significantly higher among women who had diagnosis delay of >3 months following recognition of first breast cancer symptom(s) and diagnosed at an advanced-stage. On the contrary, the risk of death was significantly lower among women who received surgical treatment and hormonal therapy.

The two-year overall survival rate (75.2%) in our cohort was higher than the survival rate reported in the rural part of Ethiopia (53%) [18]. The observed improvement could be due to the higher rate of early-stage diagnosis of breast cancer in the Addis Ababa (35.7%) than the rural part of Ethiopia (15%) [18], and better access to treatment in our cohort than their rural counterparts as well as advancement of breast cancer treatment, such as endocrine therapy over the last five years.

The survival rate in our cohort is comparable with the pooled estimate done to sub-Saharan African countries [10], where Joko-Fru et al. estimated overall survival of 84.1%, 61.4%, and 52.3% for one year, three years and five years, respectively. Our estimate is, however, lower than the survival rate recorded in other sub-Saharan African countries like Morocco (71.4% survived for five years) [184] and Libya (75.8% survived for five years) [78]. As expected, the survival rate in our cohort is lower than the global estimates. The global estimates of one-, three- and five-year overall survival rates were 92.0%, 75%, and 73%, respectively [105]. Our findings reflected that the survival rate of women with breast cancer in our country is behind some African countries [78, 184] and by far lower than the global estimates [105]. There could be several possible reasons for this discrepancy. The primary cause of the difference could be the stage at diagnosis of the women; where most of the women with breast cancer in our cohort diagnosed at an advanced-stage, and advanced-stage at diagnosis was the leading risk factor of death of

women with breast cancer [10, 40-41]. The two-year overall survival rate for women diagnosed with stage IV (26.7%) was much lower than in stage I (100.0%). Maajani et al. also found about threefold lower five-year survival among women diagnosed at stage IV (32.0%) compared to those diagnosed at stage I (86.0%) [105]. Thus, interventions targeted at downstaging the stage at diagnosis should be emphasized. In addition to the stage at diagnosis, the variation in the survival rate of women with breast cancer across these countries could be accounted to the variation in the development status of the countries [10].

Also, delayed diagnosis following symptom recognition (symptom interval of >3 months) was significantly associated with an increased risk of death. Our finding concurs with Richards and colleagues report [23]; compared to patients with delays ≤ 3 months, those patients with > 3 months delay had 12% lower 5-year survival. Unlike our findings, different works of literature [25, 111, 185] failed to detect a statistically significant relationship between the diagnosis delay and survival of the women with breast cancer. These pieces of literature, however, lacked uniformity in the definition and cut points of diagnosis interval. For instance, Smith et al. computed diagnosis interval as the "days from the first screening examination to the date of pathologic diagnosis of breast cancer" [111] while Hoffman et al. 2014 computed "from first medical contact to definitive pathologic inflammatory breast cancer diagnosis" [185]. This variation could have contributed to the inconsistent findings on the relationship between diagnosis delay and survival. Also, previous studies do not account for potential confounders, and the sample size used to calculate the excess risk of death in those patients with a delay compared to those without may not have been large enough to detect a significant difference.

On the other hand, the aggressiveness of the tumor could mask the effects of delay on survival because those patients who sought medical care early after recognition of the symptoms may be those with more aggressive forms of the disease [25] because fast-growing and aggressive cancers may receive quick attention by the patients and their physicians resulting in short delays [107]. Richards et al. [108] found a protective relationship (HR= 0.87, 95% CI [0.77, 0.97]) between delay and survival. Lastly, date of symptom recognition is subjected to recall and social desirability bias. In our study, we have restricted to incident cases and used trained enumerators.

In addition to early stage diagnosis, timely initiation of appropriate treatment improved the prognosis. The risk of death was significantly lower among women who had surgical therapy, and those who took endocrine treatment. Delay in treatment initiation is significantly associated

with an increased rate of death [186]. For example, Yu et al. found a 15% increased hazard of death among women who initiated adjuvant chemotherapy after four weeks of surgery [187], and Chavez-MacGregor et al. reported a 34% increased risk of death among those who started after 12 weeks of surgery [173]. We did not, however, find an association between delay to initiation of adjuvant chemotherapy and survival. This may, in part, reflect the short follow-up period and small sample size used in the sub-group analysis, making our estimation unpowered to detect a statistically significant difference in these groups.

Several studies reported the effect of molecular subtype of the tumor on the survival of the women with breast cancer [119, 188-189]; aggressive tumors may lead to death in a shorter time interval than those with slow progressing tumors. Due to the limited number of women with known hormone receptors (11.2%), we could not demonstrate the adjusted effect of the receptor status: estrogen receptor, progesterone receptor and Human Epidermal Growth Factor Receptor 2 on the survival of the cases. Similar to earlier findings [10], no evidence of significant association between age and survival was detected. This result may be due to the younger population distribution of our countries where more than half of the women are having cancer before their fifties [14, 33, 50, 138]. Also, the association could be attenuated due to the non-linear relationship between age at diagnosis and death from breast cancer, and under-reporting of age by the women. But, the age distribution pattern in our study is in line with previous literature in Ethiopia, where the median age at diagnosis ranges from 40 years to 45 years [14, 33, 50, 138]. This imply breast cancer in Addis Ababa has significant public health and societal implications given the majority of the cases are diagnosed at an advanced-stage, and half of the cases occur in women aged 41 or lower when they are raising children and supporting other family members.

This observational study showed that a negative relationship between delayed diagnosis following symptom recognition and survival of women with breast cancer. Thus, immediate diagnosis of breast cancer following first symptom recognition may help improve the overall survival rate of women with breast cancer. Also, development of standardized definitions of delays in diagnosis/treatment initiation might help to solve the uncertainty of the association between diagnosis/treatment delays and survival rate of women with breast cancer.

6. Validity and generalizability

To ensure the internal validity of our quantitative findings, we undertook different activities, starting from design to analysis that controls or minimize the role of bias, chance, and confounding factors on our findings.

The instrument for **Paper I**, we have adapted a questionnaire designed for a similar survey in Rwanda [58]. To improve the validity of this instrument, it was reviewed by local and international experts on the research subject and cancer care. Also, the questionnaire was pre-tested and modified accordingly.

Non-response bias is one of the selection biases; however, the response rate in all of our quantitative papers was reasonable, making the role of non-response bias minimal. Also, lost to follow-up bias is one of the challenges in the follow-up study. In this study, however, we have considered it during the design of the study, and we recorded multiple addresses (address of the respondent and her relatives). As a result, though the follow-up was for about two years, our study has only four individuals lost to follow-up. Thus, we can say the effect of lost to follow-up bias to our estimates is minimal.

The anticipated information biases in this study were interviewer and recall bias. To minimize the risk of interviewers' bias, we used experienced and trained data enumerators. The enumerators received training on objectively asking and recording the responses without showing agreement, disagreement or surprise. To mitigate the risk of recall bias, especially the date of first symptom recognition and medical consultation, we restricted our study participants to those women newly diagnosed for breast cancer and used local events like festivals and holiday to recall the date of first symptom recognition and clinical presentation. We additionally performed a sensitivity analysis and found no statistically significant difference in the association results (Adjusted prevalence ratios) and the proportions of women across the different cut points of time intervals, except for those who waited for less than a month and more than a year before the consultation. This may be because exclusion of those women who did not remembered the date of first symptom recognition or first medical consultations pooled the estimates to the lowest time intervals because they were more likely to be late presenters (have the highest waiting interval). Thus, we would not expect our estimation strategy to bias our results in a particular direction.

The interviews were conducted in a hospital setting, which could have resulted in a social desirability bias leading to under-reporting of patient delay and over-reporting of desirable behavior such as breast self-examination. To reduce the effect of this bias, we emphasized with the data collectors during training to strictly explain the purpose of the study to the respondents, and be conscious while interviewing the respondents.

Experts in the field, Oncology residents abstracted clinical data, but patients' medical charts may not document all the respondents' treatment modalities and their prognosis. To minimize this, we have triangulated the receipt of treatment from the study participants via phone interviews. Death was ascertained via phone interviews with their next of kin. Even though estimation of death affected a lesser extent, information on the treatment status of some of the dead women was difficult to ascertain via the phone interview, which could affect our effect size calculation in the multivariable analysis. Also, the proportion of late-stage at diagnosis was computed from those with the known stage. But, stage at diagnosis was missing for a small proportion of the cases (n=35, 7.9%), and there was no significant difference in the socio-demographic and clinical characteristics of patients with a known and unknown stage at diagnosis.

Pathologic staging is the most accurate, which determines treatment and prognosis of the patient. Our analysis was based on clinical staging rather than pathologic staging because nodal status in pathology reports was missing for most patients [138]. Among those patients with information on nodal status, pathologic staging was difficult since most patients (67.0%) had <10 lymph nodes removed/identified from the surgical specimen. Clinical staging, however, likely provides a good approximation of pathological staging [190] in Ethiopian settings as most patients are diagnosed at advanced-stage of the disease.

Like most studies [83, 109-112, 115], we calculated the survival from the date of diagnosis. In doing so, the survival rate might be affected by the lead time bias; survival will be shorter for these cases whose diagnosis is delayed, resulting in a shorter time of survival. We have also calculated the survival from symptom recognition to the last follow-up. The overall survival rate is by far higher if computed from the first symptom recognition date.

To minimize the role of chance for the explanation of observed effect measures of the associations, we have tested the hypothesis using a statistically significant test (p-value < 0.05) and a 95% CI. The hypothesis testing was done using appropriate data analysis methods after

checking the assumptions of each of the analysis methods used. For **paper I and III**, Poisson regression with robust variance estimator was used. This modeling has a methodological strength over the commonly used binary logistic regression [143-144], especially if the outcome is not rare. For **paper IV**, Cox proportional hazard models since survival is a variable that has time to event dimension. Also, the sample size required to address the objectives of each of the studies was computed scientifically.

Our study also tried to address the role of confounders both at the design and analysis stage. We have tried to consider all the possible variables during data collection and controlled the confounding effects using multivariable analysis. As our study was based on primary data, we hoped most confounders were controlled, and the rate of data completeness is better, and outcome misclassification is minimal. For instance, in the previous study conducted in Addis Ababa was based on retrospective medical chart review [40], 25% of the participants' files were not found, 40% of the staging was missing, and 21% were lost to follow-up. In our study, only 7.9% (35) had no information on stage, and the medical file was not found.

Concerning our findings' generalizability, our study participants were recruited from seven health facilities in Addis Ababa, where more than 90% of all incident breast cancer cases were seen. Besides, we tried to capture all potential study participants seen outside these seven facilities by reviewing the cases reported to the city population-based cancer registry. This approach made our findings generalizable to women with breast cancer in Addis Ababa and other cities with similar settings. Nonetheless, our results might not be free of hospital access bias because our study was hospital-based. Thus, we might not capture the experience of women who solely seek care elsewhere (e.g., traditional or spiritual healers) or women who are seen only at primary care facilities and do not get to the hospital.

The qualitative finding's trustworthiness was ensured following the principles of qualitative research. Our findings are credible since the data were collected from three groups of participants, women with breast cancer, family members, and health care providers that helped to triangulate [134], and generate more comprehensive data. Also, the women participants were restricted to those only diagnosed within a year to minimize recall bias. Experienced persons did in-depth interviews. Daily debriefing among the research team was held to discuss themes and issues for exploration and verify information saturation. Also, the researcher attempted to be deep engaged with the data.

The dependability of the finding was ensured since the interviews were tape-recorded to capture all the points. Besides, field notes were written after each interview to include non-verbal cues and the researchers' reflections. Moreover, audio data were transcribed by the data collector on daily basis to maintain consistency and the context of the discussion. The accuracy of the transcription was verified by comparing the transcripts with the audio records. Computer-based data coding, NVivo^{TM} software version 11, facilitated qualitative data reduction without missing the central idea. Audio records of participants', notes taken during the interviews, and verbatim transcriptions were saved for cross-checking the process and sustaining the interpretations' consistency.

To ensure the confirmability of our findings, we have included respondents' direct expressions to avoid bias during the interpretation and analysis of results. The interviewers were not staff of the oncology department at the study; hence, they are less likely to directly influence the study setting and relations with the study participants. The findings are also transferable to other women with breast cancer in Addis Ababa and other parts of the country with similar settings since we provided a detailed description of the study context, methods, and study participant selection.

7. Strengths and limitations of the study

Our study has a number of strengths. First, to the best of our knowledge, this study is the first prospective follow-up study in Ethiopia to determine the experience of women newly diagnosed for breast cancer from the first symptom recognition through the course of survivorship care using rigorous mixed methods. Second, this work is unique in looking at a range of individual factors that might influence delay to diagnosis, the stage at diagnosis, and survival rate of women diagnosed with breast cancer using primary data obtained from women with incident breast cancer in Addis Ababa city. Third, our study tried to capture all of the incident cases so that generalization about women with breast cancer in the city will be possible. Fourth, being a prospective cohort study design allows us to test the temporal relationship between symptom interval and survival of women with breast cancer. Fifth, the inclusion of the qualitative study helped to generate comprehensive evidence on the gaps and barriers to early stage diagnosis of breast cancer in Addis Ababa from different perspectives.

Our study, however, has some limitations. First, the diagnosis date was taken from the pathology report; however, this may not reflect when the patient received the diagnosis. Second, the interviews were conducted in a hospital setting, which could have resulted in a social desirability bias leading to under-reporting of patient intervals and over-reporting of desirable behavior such as breast self-examination. Third, the study was hospital-based and might not capture the experience of women who solely seek care elsewhere (e.g., traditional or spiritual healers) or women who are seen only at primary care facilities and do not get to the hospital. Fourth, we could not compute breast cancer-specific survival because we lacked data on the causes of death; thus, our survival rate may overestimate breast cancer-related mortality rate. Fifth, our estimation of the treatment delays could be underestimated since we have computed only for the women with known date of surgery, chemotherapy initiation and completion, and radiotherapy initiation. Lastly, our follow-up time was limited for about two years of diagnosis (median follow-up=25.1 months) because of logistic and feasibility concerns. The short follow-up could affect the estimated effect sizes.

8. Conclusions

In this study, we found that substantial proportions of women with breast cancer in Addis Ababa have experienced patient and diagnostic delays attributed to modifiable patient and health care provider related factors. These factors include poor awareness about breast cancer, downplaying the importance of the first breast cancer symptoms, misconceptions about breast cancer treatment and its outcomes, preference of traditional and spiritual remedies, fear of cancer diagnosis, health care providers' oversight of the early signs, and delayed referral of women for confirmation with suggestive of breast cancer symptoms.

Almost all of the first breast cancer symptoms were self-detected, which underscored that health care providers were not conducting clinical breast examination for early detection of breast cancer among patients seeking medical care for other illnesses. Only 8% of the women thought the first symptom(s) as cancer. Many women's primary response was either going to traditional healers/spiritual activities or disregarding the first symptom(s) and waiting until the sign of progression observed. More than a third of the women waited for >3 months without seeking medical attention, 11% of them waited for over a year.

Also, after the women sought medical care, they experienced longer navigation processes before receiving diagnostic confirmation. One-fourth of the women visited more than four health care facilities before diagnosis. This increased the waiting time from consultation to diagnostic confirmation. More than two-thirds of the women waited >1 month before confirmation, 18% of them waited for more than a year.

Two-thirds of women with breast cancer in Addis Ababa, Ethiopia, were diagnosed with advanced-stage disease. It was significantly associated with traditional medicine use, patient delay of > 3 months, and diagnosis delay of > 2 months. On the contrary, the prevalence of advanced-stage at diagnosis was significantly lower among women who ever practiced breast self-examination. Despite its relevance for determining the prognosis and treatment choice, tumor characterization, like molecular type, was rarely specified. The hormone receptor status was known for only 48 of the participants. Also, pathologic lymph node staging was not adequately documented or done. Two-thirds of the participants had <10 lymph nodes removed/identified from the surgical specimen.

In addition to the delayed diagnosis, half of the women with breast cancer in Addis Ababa started first treatment after 29 days of diagnosis; one-fifth of them began after one year of first symptom(s) recognition. Also, more than half of the women with breast cancer are receiving adjuvant chemotherapy after two months of surgery, a third of the women started after three months of surgery. Only one-third of the women had received radiotherapy, 24.1% of which was palliative radiation. More than half of the women waited for >3 months following completion of adjuvant chemotherapy to receive adjuvant radiotherapy. This long delay is attributed, in part, to the presence of only one radiotherapy center for the whole country.

Only 3 in 4 women with breast cancer in Addis Ababa survived two years following their diagnosis. Delay in diagnosis following recognition of symptom(s) was negatively associated with the survival of women with breast cancer, underscoring the need to increase awareness about the importance of prompt clinical evaluation and referral for diagnostic confirmation and early detection to mitigate the disease's burden in Ethiopia and other parts of Africa.

9. Recommendations

The following recommendations are forwarded to the following responsible bodies:

To Ministry of Health and Regional Health Bureaus

- Training to the frontline health care providers on the screening, early symptoms, prompt referral for breast cancer diagnosis, and benefit of immediate treatment initiation should be given to shorten waiting time between symptom recognition and diagnosis of breast cancer.
- Regular public health campaigns that alleviate the misconceptions and enhance the community awareness on the causes, early detection methods, first symptoms, and signs, diagnosis, and treatment of breast cancer.
- Health officers should design educational programs that improve the health-seeking behavior of symptomatic women at the community level, and interventions shortening the diagnostic waiting times to downstage the stage at diagnosis and improve the survival rate of women with breast cancer in the city.
- Consider personal experiences of breast cancer survivors in the educational programs to help mitigate the communities' misconceptions and fear of cancer diagnosis.
- Health care providers should include breast health information dissemination in their routine health information dissemination program, a mechanism of monitoring the commencement of clinical breast examination, and a referral system should be in place.
- Attention to the expansion of the cancer diagnostic and treatment centers and creating a mechanism of supporting the women with low socioeconomic status to improve cancer care and outcomes.
- Guidelines on the timing of diagnosis from the first consultation to diagnosis, and diagnostic confirmation to treatment initiation, and time intervals between the different treatment modalities to help monitor breast cancer care.
- Create a mechanism of working with traditional healers to improve community awareness and medical health-seeking behavior after symptom recognition.

To health care providers

- Women need more information from their health care providers to increase their breast health knowledge and seek care immediately after recognizing any breast abnormality.

- Health care providers should advise women about breast cancer, highlight the benefits of early detection and treatment initiation, encourage the women to do regular breast self-examination, and offer clinical breast examinations.
- Early suspicion and prompt referral of women with breast abnormalities to the diagnostic center is needed to shorten the long navigation points experienced to speed up diagnosis and treatment initiation.
- Integrating breast health information dissemination and clinical breast examination in the other maternal health services is required to enhance women's awareness about breast cancer and prompt referral for confirmation following a suspicious breast abnormality.
- Adhere to the proper pathologic reporting guideline of the tumor, such as adequate lymph node staging.

Women

- Conduct regular breast self-examination for any breast abnormalities.
- Consult health care providers immediately after they recognize any breast abnormalities.
- Share their stories with other women to improve breast cancer awareness and other women's health-seeking behavior.

Future research

- The effectiveness of using breast cancer survivor as community educators to increase community awareness, and medical consultations of symptomatic women shall be tested using interventional studies.
- A qualitative study is needed to explore the traditional healers' view and practice on breast cancer diagnosis and treatment to mitigate the women's delays attributed to traditional medicine use.
- Further follow up study with longer follow-up duration is recommended to evaluate the effects of treatment waiting intervals on the survival of women with breast cancer to advance local treatment timeline guidelines.

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Appendices

Annex I: English version participant information sheet and consent form

Questionnaire ID (for supervisor): _____

Part I: Participant information sheet

Introduction: Thank you so much. My name is _____. I am doing on behalf of Addis Ababa University and American cancer society for the project entitled "P*atient and diagnosis delays and survival among women with breast cancer in Addis Ababa, Ethiopia: A follow-up study*".

Question: Please can you tell me why you come to this health facility?

_____
_____

This is a research project on women newly diagnosed with breast cancer in Addis Ababa. Breast cancer is one of the leading causes of morbidity and mortality among Ethiopian women. We are going to give you information about the research project and invite you to be part of it. 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.

Purpose of the research: Although breast cancer can be detected early and treated, most women with breast cancer in Addis Ababa and Ethiopia present very late, after the disease spread to other parts of the body. However, very little is known about the causes of their delay. Also unknown are their pathways to treatment and psychosocial wellbeing, and the financial burden of the disease on them and their families. In this study, we are planning to assess the health seeking behavior, diagnosis pathways, and survival of women newly diagnosed with breast cancer in Addis Ababa.

Participation: We are asking you and others to voluntarily participate in this study because you have been recently diagnosed with breast cancer. Over the next two years, we will have an additional questionnaire to learn about your experience related to your disease. Our study is completely interview-based and does not involve any invasive procedure.

Confidentiality: Any information that we collect about you during this research will be kept confidential. Information about your identity will be put away after re-coding your file and kept

in a secure place. Only the principal investigators will be able to link your identity with the code number, should this become necessary to assist you medically. However, all the clinical information, which is devoid of your identity, may be seen by the researchers; and if need be by ethics committees.

Benefits: The study does not have direct benefit for you but it is very important for us to find the answer to the research question which in turn benefits the society especially women and their families.

Risks: The study has no risk for the participants and interviews will be conducted in a private, dedicated office for the study.

Inducement, incentive, and compensation: This study process has no form of inducement, coercion and the study does not bring any risks that incur compensation.

Results dissemination: The researcher is responsible for the dissemination of findings in different seminars and conferences. Moreover, maximum effort will be done to publish the finding in a scientific reputable journal.

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 or clinic in any way. You will still have all the benefits that you would otherwise have at this clinic or 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 clinic will not be affected in any way.

Person to contact: You have the right to ask information that is not clear about the research context and content before and or during the research work. If you have any questions, you may ask or contact the persons stated below. You can contact them at any time, even after the study has started.

If you have any further question and in case of urgency you can contact
Mr. Alem Gebremariam (Tel. +251-910352915; E-mail: alemg25@gmail.com)
Prof. Alemayehu Worku (Tel. +251-11-551-37 15; E-mail: alemayehuwy@yahoo.com)
Dr. Adamu Addissie (Tel. +251-11-55-47319; E-mail: adamuaddissie@gmail.com)

Institutional Review Board: Address: College of Health Sciences of Addis Ababa University
Telephone: +251-115538734

Part II. Informed consent form

Title of the project: "P*atient and diagnosis delays and survival among women with breast cancer in Addis Ababa, Ethiopia: A follow-up study*"

I, the undersigned, confirm that, as I give consent to participate in the study, it is with a clear understanding of the objectives and conditions of the study and with recognition of my right to withdraw from the study if I change my mind.

I _____do herby give consent to Mr. /Mrs./Miss _____to include me in the proposed research. I have been given the necessary information about the research. I have also been assured that I can withdraw my consent at any time without penalty or loss of benefits. The proposal has been explained to me in the language I understand.

Are you willing to participate in the study?

Yes ☐ No ☐ (Terminate the interview and say thank you)

Name of the participant: _____

Name of interviewer: Dr/Mr./Mrs./Miss: _____Signature _____ Date: ___/__ / ___

Supervisor:

Dr/ Mr. /Mrs./Miss: _____ Signature: _____ Date: ___ / ___ /____

Annex II: English version study instruments for quantitative data

Part I: Breast cancer patient survey/questionnaire - I

Questionnaire ID: _____

Date of interview: _____/_____/_____

Patient's Medical Record Number _____

Pathology Number: _____ Facility pathology performed: _____

Date of pathology result reported: ___/_____/ _____

Name of the health facility_____ Department: _____

Participant Address

Sub-city: _____District: _ _____House No._____

Participant's phone number:_____

Identification of proxy

1. If you had to choose, which person would you say knows best how you are doing since your cancer diagnosis? So that we may contact them in the future, may I have their phone number?
   I. Name_____phone number_____ Relationship _____
   II. Name_____ phone number_____ Relationship _____
   III. Name_____ phone number_____ Relationship _____
2. In the future if we are unable to reach you, may we have your permission to speak with any of these persons to find out how you are doing?
   0- No
   1- Yes

1. Socio-demographic characteristics of the participants

Q.No.	Questions	Choices	Skip to question
101.	How old are you?	_____years	
102.	What is your ethnicity?	_____	
103.	What is your religion?	1. Christians 2. Islam 88. Others, specify _____	
104.	Participants highest level of education obtained	1. Can't read and write 2. Can read and write 3. Elementary (Grade 1-8th) 4. Secondary (Grade 9-12th) 5. Diploma 6. Bachelor's Degree 7. Masters and above	
105.	Participant's occupation	1. Housewife 2. Government employee 3. Private employee 4. Merchant 5. Daily laborer 6. Student 7. Pensioned 88. Other **(specify)**_____	
106.	What is your current marital status?	1. Married 2. Single 3. Divorced 4. Separated 88. Others, specify_____	**Q109**
107.	Partner's educational level	1. Can't read and write 2. Can read and write 3. Elementary (Grade 1-8th) 4. Secondary (Grade 9-12th) 5. Diploma 6. Bachelor's degree 7. Masters and above	
108.	Partner's occupation?	1. Government employee 2. Private employee 3. Daily laborer 4. Merchant 5. Student 6. Has no job 7. Pensioned 88. Other **(specify)**_____	

109.	Number of individuals that live in your household including yourself	_____(number)	
110.	Including income provided by you, your spouse and others you regard as a family who lives in your household, what was your total average **monthly** household income (from all sources)	1. 600 birr and less 2. 601 - 1,650 birr 3. 1,651 - 3,200 birr 4. 3,201 - 5,250 birr 5. 5,251 - 7,800 birr 6. 7,801 - 10,900 birr 7. More than 10,900 birr 100. I do not know it	
111.	How do you pay your medical care expenses?	1. Out of pocket 2. Free medical care 3. Government insurance 4. Private insurance 5. Employing organization	**Go to Q113**
112.	What percent of your medical expenses is covered by insurance?	_____ %	
113.	Have you ever give birth?	0- No 1- Yes	**Go to Q. 201**
114.	How many children do you have?	_____(number)	

2. Participants' pre-diagnosis history of women with breast cancer

Q. N	Questions	Choices	Skip to question
201.	Do you have any medically confirmed chronic medical conditions?	0. No 1. Yes	**Q. 203**
202.	Which of the following medical conditions do you have? **(Multiple responses possible)** **Read each of listed diseases**	No Yes 1. Diabetes 0 1 2. Hypertension 0 1 3. Heart disease 0 1 4. Tuberculosis 0 1 5. Kidney disease 0 1 88. Others specify _____ A. _____ B. _____ C. _____	
203.	Have any of your relatives ever been diagnosed with breast cancer?	0. No 1. Yes 99. Refused 100. I do not know	**Q. 205**

204.	If yes, relationship with the patient? **Check all that apply**	1. Mother 2. Sister 3. Daughter 88. Others, specify_____	
205.	Have you ever heard of breast cancer before your first symptom?	0. No → **Q. 207** 1. Yes	
206.	If so, how did you learn about breast cancer? **(Multiple answers are possible)** **(Read the options)**	1. Mass media (TV, radio, internet) 2. Health care provider 3. Friend/family/ neighbors 88. Other specify: _____	
207.	Before you feel/saw the first symptom/sign of your breast problem, did you know how to examine your breasts using your hand for lumps?	0. No 1. Yes	
208.	Before you feel/saw the first symptom/sign of your breast problem, did you ever examine your breast using your hand for lumps?	0. No 1. Yes	
209.	Before you feel/saw the first symptom/sign of your breast problem, did a doctor or nurse ever examine your breast for a lump?	0. No 1. Yes	
210.	Before you feel/saw the first symptom/sign of your breast problem, did you have a mammogram (a machine to look for a lump or other abnormalities in your breast)?	0. No 1. Yes	
211.	When did you first noticed the symptoms of your breast problem?	____/ _____/ _____ dd/mm/yyyy (pleas identify any information that the patient can provide, whether a full date, a month and year, or the year only)	
212.	If you do not remember the month, but remember the year, was it the beginning, middle, or end of the year?	1. Beginning 2. Middle 3. End 4. Don't know the year	

213.	What was the symptom you first noticed? **Multiple response is possible** **Read the options**	1. Breast pain 2. Breast mass 3. Nipple discharge 4. Breast skin color changes 88.Other, specify: _____	
214.	Were you pregnant when you first recognized the symptom(s)?	0. No 1. Yes	
215.	Were you breastfeeding when you first recognized the symptom(s)?	0. No 1. Yes	
216.	Who discovered the first symptom(s)?	1. Self 2. Husband 3. Health care provider 88. Others, specify _____	
217.	What was your immediate impression/suspicion of the first symptom(s)?	1. Mitch 2. Tumor 3. Cancer 4. Nothing 88. Others, specify_____	
218.	What was your immediate action for the first symptom(s)?	1. I did nothing 2. I went to the health facility immediately 3. I went to traditional healers 4. I performed ritual activities 88. Others, specify _____	
219.	Did you see a traditional healer after you recognized the first symptom(s) but before diagnosis of your problem?	0. Yes 1. No 99. Refused	**Q221**
220.	If yes, can you describe it?	_____ _____ _____ _____	
221.	Were there any spiritual activities that you have done for your symptom(s) after you recognized the first symptom(s) but before diagnosis of your problem?	0. Yes 1. No 99. Refused	**Q223**

222.	If yes, can you tell me what you did? **Multiple responses possible** **Read the options**	1. Holy water 2. Praying 88. Others, specify _____	
223.	When was the **first time** you visited a health facility for your breast cancer?	____/_____/_____ dd/mm/yyyy	
224.	If you do not remember the month, but remember the year, was it the beginning, middle, or end of the year?	1. Beginning 2. Middle 3. End 4. Don't know the year	
225.	Which level of health facility did you first visit for your problem?	1. Health center 2. Public hospital 3. Private hospital 4. Private clinic	
226.	Did you experience additional symptom(s) before you went to the health care provider?	0. No → **Q. 228** 1. Yes	
227.	If yes, what were the additional symptom(s) you experienced? **Multiple response possible** **Read options**	1. Pain 2. Lumps 3. Itching or burning 4. Nipple discharge 88. Other, Specify:_____	
228.	What motivated (triggered) you to see a health care provider for your symptom(s)?	1. First symptom 2. Additional symptom(s) 3. Family member(s) 4. Friend(s) 5. A provider secondary to other care 88. Other, Specify_____	
229.	When was the time pathology report documented for confirmation of your breast problem? **(See the pathology results report date and put correctly)**	____/ ____/_____(dd/mm/yyyy)	
230.	How many health facilities did you visit before you received a final diagnosis for your problem?	_____ health facilities	
231.	How many times did you go to a health facility before you received a final diagnosis for your problem?	_____times	
For women who delayed more than three months before seeking medical care at a health center or hospital **(if not end survey one)**			

232.	What was the single most important factor that prevented you from seeking medical care sooner?	_____ _____	
233.	Did any of the following prevent you from seeking medical care at a health center or hospital sooner? **Read the choices and circle all that apply**	1. I was not bothered by the problem at first 2. I was too busy at home or my job 3. I was afraid of being examined by a doctor or other health provider 4. I was afraid of examination results 5. I was afraid of the treatments, including potentially losing my breast 6. I visited a traditional healer first 7. I did not know where an appropriate medical facility was 8. I did not want anyone knowing I had a breast problem 9. I thought treatment might be too expensive 88. Other, specify: _____	

Part II: Breast cancer patient survey questionnaire - II

Questionnaire ID: _____ Date of interview: _____/_____/_____
Patient's Medical Record No. _____ Participant's phone number: _____
Primary relative's phone number:_____Relationship:_____

Name of interviewer: Dr/ Mr. /Mrs./Miss: _____Date: _____/_____ / _____

2. 1. Treatment status of women with breast cancer

Q. N	Statements	Choices	Skip to question
201.	Have you received any treatment for you cancer?	0. No → 1. Yes	**Q204**
202.	If yes, what kind of treatments you have received? (**multiple answer is possible**)	1. Surgery 2. Chemotherapy 3. Radiation therapy 4. Hormone therapy 88. Other forms of treatment; specify: _____	
203.	Where (in which facility) did you receive these treatments?	_____ _____	
204.	Since you were diagnosed with the disease, were you unable to receive any form of treatments?	0. No → 1. Yes	**Q206**
205.	What were **the main reasons for not receiving the** treatment? **Multiple response is possible**	1. Could not afford the price of the treatment 2. Treatment not locally available 3. Waited too long to get it 4. Difficulty in getting appointments 5. Do not like or trust or believe in doctors 6. Insurance did not cover 7. Did not know where to go for treatment 88. Others; specify _____	

2.2.Use of traditional medicine after they have diagnosed

S.N	Question	Choices	Skip to question
206.	Have you seen a traditional healer other than your regular doctors?	0. No → 1. Yes	**Q301**
207.	If **yes**, what type of healer did you see?	1. Herbalist 2. Spiritual healer 88. Other, specify_____	
208.	What is your main reason for using this therapy? **Multiple answer is possible**	1. To treat my cancer 2. To lessen the side effects of cancer treatment 3. To relieve symptoms of my cancer 4. To relieve stress 88. Other: specify:_____	

2.3. Participants completion of chemotherapy and hormonal therapy

S. N	Questions	Choices	Skip to question
301.	Have you taken chemotherapy?	0. No → 1. Yes	Q 305
302.	If yes, how many cycles did your doctor ordered?	_____ number 99. I do not know	
303.	Did you finish all the cycles?	0. No 1. Yes →	Q305
304.	If **no**, what are the main reasons?	1. I forget to keep treatment appointments 2. I could not tolerate the side effects 3. I could no longer afford the treatment 4. I did not trust the effectiveness of the medicine 5. The drug was not available 88. Others, specify_____	
305.	Are you taking hormonal therapy?	0. No → 1. Yes	End
306.	Have you ever missed taking your hormonal therapy?	0. No → 1. Yes	End
307.	If yes, for how long you missed?	_____	
308.	What was your main reason for missing taking the drug?	1. Side-effects 2. Financial 3. Drug not available 4. I forget to take 88. Others, specify_____	

Is there anything else you would like to tell us about your experiences with cancer?

Thank you for participating in this important study!

Part III: Clinical data extraction form

Questionnaire ID: _____

Patient's Medical Record No. _____

Name of data extractor: _____

Date of data extraction: _____/_____/_____ Age of the women: _____

1.1. Clinical characteristics of women with breast cancer

Q. N	Statements	At diagnosis	During initiation of treatment	Current status (response assessment)
1.	Date of diagnosis (Histology/FNAC)	_____/_____/_____	NA	NA
2.	Tumor type –histology	_____	NA	NA
3.	Receptor status	ER ____ PR ____ HER2 _____ (Date: ____/___/ _____)	NA	NA
4.	Grade	_____ (Date: ____/___/ _____)	NA	NA
5.	Surgical margin status			
6.	Lymphovascular invasion			
7.	Tumor size (diameter)	____ centimeter	____ centimeter	____ centimeter
8.	T staging (clinical)	T1 T2 T3 T4 (Date: ____/___/ _____)	T1 T2 T3 T4 (Date: ____/___/ _____)	
9.	Lymph node status (clinical)	N1 N2 N3 (Date: ____/___/ _____)	N1 N2 N3 (Date: ____/___/ _____)	N1 N2 N3 (Date: ____/___/ __)

10.	Pathology stage	T=_____ N=_____ No. of Node identified=_____ No. of positive node= _____ (Date: ____/___/ _____)		
11.	Metastasis (if **Yes**)	Site1_____Date_____ Site2_____Date_____ Site3_____Date_____	Site1_____ date_____ Site2_____ date_____ Site3_____ date_____	Site1____ date_____ Site2_____date_____ Site3_____date_____
12.	Group stage of the disease	_____ (Date: ____/___/ _____)	_____ (Date: ____/___/ _____)	_____ (Date: ____/___/ ____)
13.	Recurrence for those who undergone MRM (if **Yes**)	NA	Site_____ (Date: ____/___/ _____)	Site_____ (Date: ____/___/ _____)
14.	Comorbidities (if **Yes**, list type and date)	_____ (Date: ____/___/ _____)	_____ (Date: ____/___/ _____)	_____ (Date: ____/___/ _____)
15.	Hemoglobin level (mg/dl)	_____mg/dl	_____ mg/dl	_____ mg/dl
16.	HIV status (Positive/Negative /not screened)	_____ (Date: ____/___/ ____)	_____ (Date: ____/___/ ____)	_____ (Date: ____/___/ ____)
17.	If HIV positive, is she taking HAART (yes/no)	Yes No Not-documented		

MRM: Modified radical mastectomy, HAART: Highly active antiretroviral therapy,

1.2. Treatment status of women with breast cancer

S.N	Treatment	Treatment	Date of treatment initiated	Date of treatment completion	Date event documented
1.	Surgery (if **YES**)	Type of surgery_____	___/___/____	NA	
2.	Chemotherapy (if **Yes**)		___/___/____	___/___/____	
2.1	Chemotherapy regimen	_____	NA	NA	
2.2.	Number of cycles planned	_____	NA	NA	
2.3.	Number of cycles received	_____	NA	NA	
3.	Radiotherapy (if **Yes**)		___/___/____	___/___/____	
3.1.	Dose/fractionation	_____	NA	NA	
3.2.	Aim of radiotherapy (palliative, adjuvant)	_____	NA	NA	
4.	Hormonal therapy (if **Yes**)		___/___/____	NA	
4.1.	Type of hormonal therapy	_____	NA	NA	
5.	Other form of treatments	_____	NA	NA	
6.	Date of last contact/follow-up	_____/ _____/ _____ (dd/mm/yyyy)			

NA: Not applicable

Annex III: English version study instrument for qualitative data

Part I: Participants information sheet and informed consent form

Introduction: Thank you for agreeing to speak with me today. My name is _____. I come from Addis Ababa University, School of Public Health to interview breast cancer patients, family members and health care providers. Breast cancer is the leading cause of morbidity and mortality among Ethiopian women. Early identification and treatment are the main interventions of premature death from breast cancer.

Purpose of the research: Despite the disease is the most common cancer in Ethiopian women, patients present to health facility very late after the disease gets advanced. However, very little is known about the causes of their delay. We are conducting this study with the aim of exploring the barriers to early diagnosis of breast cancer. In this endeavor we want to learn from your experience as to how you managed your illness and barriers to early diagnosis so that it will help us to learn about the barriers and further can help to design interventions to improve early detection of breast cancer in Ethiopia.

Participation: I am asking you and others to voluntarily participate in this study because you have been diagnosed to have breast cancer, or family member or health care provider.

Risks: The study has no any risk for the participants and interview will be private to make safe participants from any fear. It is completely interview based; it has no any invasive procedure.

Benefits: You will not gain any direct benefit for being participated. But your participation is very important for us to learn about the barriers and find the answer to the research question which in turn benefits the society specially women.

Confidentiality: Any information that I collect about you during this interview will be kept confidential. Information about your identity will be put away after re-coding your file; and kept in a secured place. Only I will be able to link your identity with the code number.

Inducement, incentive, and compensation: This study process has no form of inducement, coercion and the study does not bring any risks that incur compensation.

Results dissemination: The researcher is responsible for the dissemination of findings in different seminars and conferences. Moreover, maximum effort will be done to publish the finding in a scientific reputable journal.

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 or clinic in any way. You will still have all the benefits that you would otherwise have at this clinic or 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 clinic will not be affected in any way.

Person to contact: You have the right to ask information that is not clear about the research context and content before and or during the research work. If you have any questions, you may ask or contact the persons stated below. You can contact them at any time, even after the study has started.

If you have any further question and in case of urgency you can contact

Mr. Alem Gebremariam (Tel. +251-910352915; E-mail: alemg25@gmail.com)

Prof. Alemayehu Worku (Tel. +251-11-551-37 15; E-mail: alemayehuwy@yahoo.com)

Dr. Adamu Addissie (Tel. +251-11-55-47319; E-mail: adamuaddissie@gmail.com)

Institutional Review Board: Address: College of Health Sciences of Addis Ababa University

Telephone: +251-115538734

Part II: Consent form

I, the undersigned, confirm that, as I give consent to participate in the study, it is with a clear understanding of the objectives and conditions of the study and with recognition of my right to withdraw from the study if I change my mind.

I _____ do herby give consent to _____ to be interviewed. I have been given the necessary information about the research. I have also been assured that I can withdraw my consent at any time without penalty or loss of benefits. The proposal has been explained to me in the language I understand.

Participant's signature: _____Date: _____/_____/_____

Name of interviewer: Mr./Mrs.: _____Date: _____/_____ / _____

Thank you for agreeing to participate in this in-depth interview

The interview will take about an hour. I would like to ask your permission for taping the session because I do not want to miss any of your ideas and suggestions. Although I am going to take some notes during the session, I cannot possibly write fast enough to get it all down. I want to note again that the information you provided will be confidential. Any information we use from your interview will be combined with information from other women with breast cancer/family members/health care providers. It will not be possible to identify what you have said.

Do you have any questions before we start the interview?

Participants' profile

Age:_____
Marital status: ___
Level of education: _____
Occupation: _____

Part III: Interview guides for women with breast cancer

1. What is known about breast cancer in the community?
   Probe:
   - Causes, symptoms, screening, treatments, support
2. Have you ever heard of breast cancer before you recognized the first symptom of your illness? (when, how)
3. Tell me about your experience with breast cancer from the first symptom recognition to diagnosis

Probe:

- Who noticed the problem with your breast?
- How was noticed the problem with your breast?
- What do you feel when you notice it?
- What action was taken after the problem was known? (before and after diagnosis)
- When do you seek medical care?
- Why do you seek medical care? (appearance of symptoms/persistence of symptoms/worsening of symptoms)
- When you were told you had breast cancer?
- Who was the first person you told about your diagnosis?
- What stage was the cancer diagnosed?
- Tell me about activities that helped you during your diagnosis?

4. What are the major challenges you have faced during diagnosis?
5. Why do breast cancer patients seek medical care late? (What affected that)
   Probe:
   - Socioeconomic factors (age, education, income)
   - Individual factors (do not know where to go, carelessness/neglect, fear, financial, underestimate the severity of the problem)
   - Cultural factors (traditional medicine, community beliefs)
   - Health care system (access, referral)
6. What measures do you suggest to make sure breast cancer diagnosis happens early?

Probe:

- At individual level, community level, health facility level, government level
- What advice do you have for other women about breast cancer?

7. Do you have any questions for us or something you want to add?

Thanks for your time and information, have a good day!!!

Part IV: Interview guide for family members of breast cancer patients

1. Can you tell me about yourself?
2. What is the relation with patient?
3. Can we discuss on cancer?
   Probe:
   - What do you know about cancer?
   - How do people perceive cancer?
   - What about breast cancer?
   - Would you please tell us the local name given to cancer, if any!
   - What is the communities' perception about breast cancer? (causes, treatment, survival)
4. Can you explain me about your relative's (Patient Name) illness?
5. What was the feeling of your relative (Patient's Name) and yours when the illness was confirmed as cancer?
   Probe:
   - Who told the patient as her problem is cancer?
   - What was her immediate reaction?
6. How would your relative (Patient name) with cancer think about her disease?
   Probe:
   - for luck of hope,
   - fear of stigmatization, sexuality,
   - effect on marital status including possibility of divorce
   - how simple is to talk about cancer with the cancer patients

7. What are the major challenges your relative (Patient name) have faced during diagnosis?

8. Why the clients are not seeking medical care earlier? (What affected that)
   Probe:
   - Socioeconomic factors (age, education, income)
   - Individual factors (do not know where to go, carelessness/neglect, fear, financial, underestimate the severity of the problem)
   - Cultural factors (traditional medicine, community beliefs)
   - Health care system (access, referral)
9. What measures do you suggest to make sure breast cancer diagnosis happens early?
10. Do you have any questions for us or something you want to add?

Thanks for your time and information, have a good day!!!

Part V: Interview guide for health care providers

1. Before we start our discussion, can you tell me about yourself?
   Probe:
   - Educational background, service year, working department
2. How long have you been involved in caring or treating cancer patients?
   Probe:
   - Type of cancer cases you are mainly caring
   - Your main role in the department
3. Can we discuss on cancer?
   Probe:
   - What do you know about cancer?
   - How do people perceive cancer?
   - What about breast cancer?
   - Would you please tell us the local name given to the cancer, if any?
   - What is the communities' perception about breast cancer? (causes, treatment, survival)
4. How would patients with cancer think about the disease?
   Probe:
   - How do you communicate them about their cancer status?
   - To whom do you communicate first
   - How simple is to talk about cancer with the cancer patients?
   - How do you see the patients in terms of lack of hope, fear of stigmatization, sexuality?
5. Would you please tell us if there are issues related to disclosure of the status of a woman with breast cancer?
6. What could be the possible barriers for women to early diagnosis?
7. Do you have any questions for us or something you want to add?

Thank you very much for your time!

Annex IV: Amharic version participant information sheet and consent form

የመጠይቅ ቁጥር (በሱፐርቫዘር ይሞላል)፡ ----------

ክፍል-1፡ <u>በጡት ህመም ጥናት ለሚሳተፉ ሴቶች የተዘጋጀ የስምምነት ውል ቅፅ</u>

<u>መግቢያ፡</u> ሊያነጋግሩኝ ፍቃደኛ ስለሆኑ በጣም አመሰግናነሁ። ስሜ ---------- ሲሆን፣ እዚህ የመጣሁት፣ በአዲሰ አባባ ዩኒቨርስቲ ሕ/ሰብ ጤና አጠባበቅ ትምህረት ክፍል ና በአሜሪካ ካንሰር ሶሳይቲ በጡት ሕመም የሚደረግ ምርምር መረጃ ለመሰብሰብ ነው።

ጥያቄ፡ እባክዎን ወደዚህ የህክምና ተቋም የመጡበት ዋናው ህመምዎን ምንድን እንደሆነ ሊነግሩኝ ይችላሉ?

_____
_____

ይህ ጥናት የጡት ሕመም እንዳለባቸው በቅረቡ የታወቀላቸው በአዲስ አበባ የሚኖሩ ሴቶች ላይ የሚደረግ የምርምር ፕሮጀክት ነው። የጡት ሕመም የኢትዮጵያ ሴቶችን በዋንኛነት ለህመምና ለሞት ከሚዳርጉ በሽታዎች አንዱ ነው። ስለጥናቱ መረጃ እንሰጦታለን እንዲሁም የጥናቱ አካል እንዲሆኑ ጥያቄ እናቀርብሎታለን። በዚህ ጥናት ለመሳተፍ ወይም ላለመሳተፍ ትንሽ ጊዜ ወስደው መወሰን ይችላሉ። ከመወሰኖ በፊት ስለ ጥናቱ መወያየት ከሚፈልጉት ሰው ጋር መነጋገር ይችላሉ።

<u>የምርምሩ አላማ</u>፡- ምንም እንኳን የጡት ሕመም በጊዜ ሊገኝ እና ሊታከም የሚችል በሽታ ቢሆንም፣ ብዙ ጊዜ በአዲስ አበባ እንዲሁም በኢትዮጵያ ያሉ ህመምተኞች ወደ ህክምና የሚመጡት ቆይተውና በሽታው ወደ ሌላ የስውነት አካል ከተዛመተ በኃላ ነው። ነገር ግን ለምን እንደሚዘገዩ የሚታወቀው ነገር አነስተኛ ነው። እንዲሁም ህክምና ለማግኘት ያለፉባቸውን መንገዶች፣ የስነ-ልቦና እና የማህበራዊ ደህንነታቸው በተጨማሪም በሽታው በነሱ ላይ እንዲሁም በቤተሰቦቻቸው ያሳደረው የገንዘብ ጫና በደንብ አልተጠናም። በዚህ ጥናት ቶሎ ህክምና የመፈለግ ባህሪን፣ህክምና ለማግኘት ያለፉባቸውን መንገዶች፣ ከሕመሙና ከህክምናው ጋር ተያይዘ ህመምተኛዋ የሚናገሩዋቸው ነገሮች፣ በሽታው በገንዘብ ደረጃ ያሳደረውን ተጽኖ እንዲሁም ከጡት ህመምዎን የተያዘ እናቶች የሚገጥማቸው ችግሮች የሚዳስስ ጥናት ነው።

<u>ተሳትፎ</u>፡- የጡት ሕመም በቅርቡ ስለተገኘቦት እርሶና ሌሎችን በፍቃደኝነት ላይ የተመሰረተ ተሳትፎ እንዲያደርጉ እንጠይቆታለን። ለሁለት አመት ለምንከታተለው ጥናት በተደጋጋሚ የምንጠይቅበት መጠይቅ ይኖረናል። ጥናታችን በመጠይቅ ላይ ብቻ መሰረት ያደረገ ሲሆን ምንም አይነት ምርመራን የሚጠየቅ ነገር የለውም።

<u>ሚስጥራዊነት</u>፡- በጥናቱ ወቅት ስለ እርስዎ የምንሰበስበው ማንኛውም መረጃ ሚስጥራዊነቱ የተጠበቀ ነው። እርስዎን የሚገልጽ መረጃ ሌላ መለያ ቁጥር ከተሰጠው በኃላ ለብቻው ማንም እንዳያገኘው ሆኖ ይቀመጣል። የጥናቱ ዋና ተመራማሪዎች ብቻ እርስዎን በህክመናው እንዲረዱ የሚያስፈልግ ነው ብለው ካመኑ፣ የተሰጠውን መለያ ቁጥር የእርስዎን ማንነት ለመለየት ሊጠቀሙበት ይችላሉ። ነገር ግን የእርስዎን ማንነት ሳይገለጥ ከህክምናው ጋር ተያይዘ ያሉ መረጃዎች በተመራማሪዎች እንዲሁም ከአስፈለገ በስነ-ምግባር ኮሚቴ ሊታይ ይችላል።

<u>ከጥናቱ የሚገኘው ጥቅም</u>፡- ለእርስዎ ቀጥታዊ የሆነ ጥቅም ባይኖረውም፣ የእርስዎን በጥናቱ ተሳታፊ መሆን በጥናቱ ላይ የተጠቀሱትን ጥያቄዎች ለመመለስና ለወደፊት የሕብረተሰቡ በተለይም የሴቶች ጤና መሻሻል ከፍተኛ አስተዋፅዖ ያደርጋል።

<u>ተጋላጭነት</u>፡- ጥናቱ በምንም መልኩ የጥናቱን ተሳታፊ ተጋላጭ አያደርገውም። እንዲሁም መጠይቁ ለብቻ ለዚህ መጠይቅ ተብሎ በተዘጋጀ ቢሮ የሚደረግ ነው።

<u>ያለመሣታፍ ወይም ከጥናቱ የማቋረጥ መብት፡</u> በዚህ ጥናት መሳተፍ ካልፈለጉ ያለመሳተፍ ሙሉ መብት አለዎት። እንዲሁም ያለመሳተፍዎ በዚህ ሆስፒታል በሚያገኙት ሕክምና ላይ ምንም አይነት ተጽኖ አያሳድርም። በዚህ ሆስፒታል የሚያገኙት ማንኛውም ጥቅም እንደተጠበቀ ይሆናል። እንዲሁም ጥናቱ ላይ መሳተፍ ከጀመሩ በኃላ በማንኛውም ጊዜ እንደታካሚ በዚህ ሆስፒታል ያለዎትን መብት ሳያጡ የማቋረጥ መብትዎን የተጠበቀ ነው። በማንኛውም ሁኔታ በዚሕ ክሊኒክ ውስጥ የሚያገኙት ህክምና በዚህ ጥናት ውስጥ በመሳተፍዎ ወይም ባለመሳተፍዎን የሚቀየር ነገር አይኖረውም።

<u>ግፊት፣ ማበረታቻ፣ካሳ፡</u> ይህ ጥናት ተሳታፊው ላይ የሚያሳድረው ምንም አይነት ተጽኖም ይሁን ግፊት ይሁን በጥናቱ እንዲሳተፉ የሚሰጥ ማበረታቻ የለውም። ጥናቱ ለካሳ መስጠት ያሚደርስ ምንም ጉዳት የለውም።

<u>የጥናቱ ውጤት ስርጭት፡</u> ተመራማሪው የጥናቱን ውጤት በተለያዩ ማሰራጫ መንገዶች፣ በሰሚናር፣ ኮንፈረንስ የማሰራጭት ሀላፍነት አለው። እንዲሁም የጥናቱ ውጤቶች በአለም ኣቀፍ የምርምር መጂሄቶች እንዲታተሙ ይደረጋል።

<u>ስለ ጥናቱ ተጨማሪ መረጃ ከፈልጉ፡-</u> ማንኛውም ጥያቄ ካሎት ከዚህ በታች የተጠቀሱትን ሰዎች ማነጋገር ይችላሉ። በማንኛውም ጊዜ ልታነጋግሩዋቸው ትችላላችሁ። በኋላም ላይ ማንኛውም ጥያቄ ካለችሁ፣ የጥናቱን ተመራማሪዎች ከታች በተጠቀሱት አድራሻዎች ማግኝት ይችላሉ።

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የተቋሙ፡ ጥናቱን፡ የሚመለከት፡ ኮሚቴ
አድራሻ፡ አዲስ አበባ ዩንቨርስቲ የጤና ሳይንስ ኮሌጅ
ስልክ፡ +251- 118-96-13-96

<u>ክፍል 2፡ የስምምነት ውል ቅጽ</u>
እኔ ከዚህ በታች ስሜ የተገለጸው የዚህን ጥናትን አላማ በመገንዘብ እንዲሁም ሀሳቤን ከቀየርኩ የመውጣት መብት እንዳለኝ በማወቅ በዚህ ጥናት ለመሳተፍ መስማማቴን አረጋግጣለሁ።
እኔ _____ ለወ/ሮ/ለወ/ሪት/ሲ/ር _____ በዚህ ጥናት ለመሳተፍ መስማማቴን እገልጻለሁ። ስለጥናቱ አስፈላጊው መረጃ ተሰቶኛል። እንዲሁም በፈለኩት ጊዜ ካለ ምንም ቅደመ ሁኔታ ወይም የማገኘው የህክምና ድጋፍ ላይ ተጽኖ ሣያሳደር ከጥናቱ ማቋረጥ እንደምችል ተረጋግጦልኛል። በሚገባኝ ቋንቋ ስለ ጥናቱ መግለጫ ተደርጎልኛል።

በጥናቱ ለመሳተፍ ፍቃደኛ ኖት?
አዎ ☐ አይደለሁም ☐ **(አይደለሁም ካሉ ኣመስግነው ቃለ-መጠይቁን እዚህ ላይ ያቁሙ)**

የተሳታፊ ስም፡ _____

ቃለ-መጠየቁን ያደረገው ሰው ስም፡ ወ/ሮ/ወ/ሪት/ሲ/ር _____ቀን___/___/___

ተቆጣጣሪ (ሱፐርቫይዘር)

ዶ/ር/አቶ/ወ/ሮ/ወ/ሪት _____ፊርማ፡ _____ቀን፡___/___/___

Annex V: Amharic version study instruments for quantitative data

ክፍል 1፡ የጡት ሕመም መጠይቅ አንድ

የመጠይቅ ቁጥር (በሱፐርቫዘር ይሞላል)፡ _____

ቃለ-መጠይቅ የተደረገበት ቀን፡ ____/_____/_____ (ቀን /ወር/ዓ.ም) ሠዓት፡ _____ እሰከ _____

የተሳታፊ የህክምና መዝገብ ቁጥር፡ _____ የፓቶሎጂ ውጤት የተገኘበት ቀን፡ ____/_____/_____

የተሳታፊ የፓተሎጂ ቁጥር፡ _____ የተሰራበት ጤና ተቋም፡ _____

መጠይቁ የተሞላበት ጤና ተቋም ስም _____ ክፍል/ዲፓርትመንት፡ _____

የተሳታፊዎች አድራሻ

ክ/ከተማ_____ወረዳ _____የቤት ቁጥር፡_____

የተሳታፊ ሞባይል ቁጥር፡ _____

የተሳታፊ የቅርብ ዘመድ መለያ

1. የጡት ሕመም ከተገኘቦዎት በኋላ ስለ እርስዎ ሁኔታ በደንብ የሚያውቁ ሰዎች መምረጥ ቢኖርቦት እነማን ናቸው? ምናልባት ወደፊት እነሱን ማናገር ቢኖርብን ስም እንዲሁም ስልክ ቁጥር ሊሰጡኝ ይችላሉ?
    1. ስም _____ ስልክ ቁጥር_____ ዝምድና _____
    2. ስም _____ ስልክ ቁጥር_____ ዝምድና _____
    3. ስም _____ ስልክ ቁጥር_____ ዝምድና _____
2. ወደፊት ከእርስዎን በተጨማሪ ከላይ ከተጠቀሱ ሰዎች ማህል አንዳቸውን ስለ እርስዎ ሁኔታ እንድናናግር ይፈቅዱልናል?

    0- አልፈቅድም

    1- አዎ

1. **የጥናቱ ተሳታፊዎች ስነ-ህዝባዊ መረጃ**

ጥ.ቁ	ጥያቄ	አማራጭ	ወደ ጥ. ቁጥር
101.	እድሜዎት ስንት ነው?	_____ አመት	
102.	ብሄርዎ ምንድን ነው?	_____	
103.	ሀይማኖትዎ ምንድን ነው?	1. ክርስቲያን 2. ሙስሊም 88. ሌላ ጥቀስ_____	

104.	የትምህርት ደረጃዎ ሊነግሩኝ ይችላሉ?	1. ማንበብና መጻፍ የማይችሉ 2. ማንበብና መጻፍ የሚችሉ 3. አንደኛ ደረጃ (1-8ኛ ክፍል) 4. ሁለተኛ ደረጃ (9-12ኛ ክፍል) 5. ዲፕሎማ 6. ዲግሪ 7. ማስተርስ እና ከዛ በላይ	
105.	ስራዎን ምንድን ነው?	1. የቤት እመቤት 2. የመንግስት ተቀጣሪ 3. የግል ተቀጣሪ 4. ነጋዴ 5. የቀን ስራተኛ 6. ተማሪ 7. ጡረተኛ 88. ሌላ ከሆነ ይጠቀስ_____	
106.	በአሁኑ ግዜ የጋብቻ ሁኔታዎ ምንድን ነው ?	1. ያገቡ 2. ያላገቡ 3. የፈቱ 4. ባል የሞተበት 88. ሌላ ከሆነ ይጠቀስ_____	**ወደ ጥ. 109 ይሂዱ**
107.	የባለቤትዎ የትምህርት ደረጃ ሊነግሩኝ ይችላሉ?	1. ማንበብና መጻፍ የማይችሉ 2. ማንበብና መጻፍ የሚችሉ 3. አንደኛ ደረጃ (1-8ኛ ክፍል) 4. ሁለተኛ ደረጃ (9-12ኛ ክፍል) 5. ዲፕሎማ 6. ዲግሪ 7. ማስተርስ እና ከዛ በላይ	
108.	የትዳር ጉዋደኛዎ የስራ ሁኔታ ምንድን ነዉ?	1. የመንግስት ተቀጣሪ 2. የግል ተቀጣሪ 3. የቀን ስራተኛ 4. ነጋዴ 5. ተማሪ 6. ስራ የላቸውም 7. ጡረተኛ 88. ሌላ ከሆነይጠቀስ_____	
109.	እርስዎን ጨምሮ በቤትዎ ወስጥ ስንት ሰው ይኖራል?	_____	
110.	የቤትዎ የወር ገቢ በአመካኝ ስንት ነው? (የእርስዎን፣ የባለቤትዎን እንዲሁም በቤትዎ የሚኖሩ የቤተሰብ አባል ገቢ ጨምሮ) **እያንዳንዱ ምርጫ ይነበብ**	1. 600 ብር ና ከዛ በታች 2. ከ 601 - 1,650 ብር 3. ከ 1,651 - 3,200 ብር 4. ከ 3,201 - 5,250 ብር 5. ከ 5,251 - 7,800 ብር 6. ከ 7,801 - 10,900 ብር 7. ከ 10,900ብር በላይ	

		100. አላውቅም	
111.	የህክምና ወጪዎን እንዴት ነው የሚሸፍኑት?	1. ከራሴ ኪስ 2. የነጻ ታካሚ ነኝ 3. የመንግስት የጤና መድህን አለኝ 4. የግል የጤና መድህን አለኝ 5. የተቀጠርኩበት ድርጅት ይከፍልልኛል	**ወደ ጥ. 113 ይሂዱ**
112.	ስንት በመቶ የሚሆን የህክምና ወጪዎ ይሸፈንሎታል?	---------- %	
113.	ልጅ ወልደው ያውቃሉ?	0- አላውቅም 1- አዎ	**ወደ ክፍል 2 ይሂዱ**
114.	ስንት ልጆች አሎት?	----------ቁጥር	

2. የተሳታፊዎች የጡት ህመም እንዳለቦት ከመታውቁ በፊት የነበረው የተሳታፊዋ የጤና ሁኔታ በተመለከተ የሚዳስሱ መጠይቆች

ጥ.ቁ	**ጥያቄ**	**አማራጭ**	**ወደ ጥ. ቁጥር**
201	በሕክምና የተረጋገጡ/ጡ ለረጅም ጊዜ ሊቆዩ የሚችሉ ማንኛውም በሽታ አሎት ተብለው ያውቃሉ?	0- የለኝም 1- አዎ	**ወደ ጥ. 203 ይሂዱ**
202	**መልስዎ አዎ ከሆነ** የበሽታው አይነት ምንድን ነው? **(ከአንድ በላይ መልስ ይቻላል)፤** **(የያንዳንዱን የተጠቀሰው ምርጫ ያንብብላቸው)**	**አይ አዎ** 1. የስካር በሽታ 0 1 2. ደም ግፊት 0 1 3. የልብ በሽታ 0 1 4. ሳንባ ነቀርሳ 0 1 5. የኩላሊት በሽታ 0 1 88. ሌላ ካለ ይገለጽ ሀ. ለ. ሐ.	
203	ከቤተሰብዎ መሀል እንደ-እርስዎ የጡት ሕመም ተገኝቶበት የሚያውቅ ሰው አለ/አሉ?	0- የሉም 1- አዎ 99. መመለስ አልፈልግም 100. አላውቅም	**ወደ ጥ. 205 ይሂዱ**
204	**መልስዎ አዎ ከሆነ** ከታማሚው ጋር ያሎዎት ዝምድና ምንድን ነው? **(ከአንድ በላይ መልስ ይቻላል)**	1. እህት 2. እናት 3. ሴት ልጅዎ 88. ሌላ ይግለጽ_____	
205.	የበሽታውን **ምልክት ከማየትዎ በፊት** ስለ	0- አላውቅም	**ወደ ጥ. 207**

	ጡት በሽታ ሰምተው ያውቃሉ?	1- አዎ	**ሂዱ**
206.	**ሰምተው ካወቁ፣** ከየት ነው የሰሙት? (**ከአንድ በላይ መልስ መስጠት ይቻላል)** (ሁሉም ምርጫዎች ይነበቡ)	1. ከመገናኛ ብዙሀን (ቴሌቪዥን፣ ኢንተርኔት፣ራዲዮ) 2. ከጤና ባለሙያ 3. ከጉዋደኛ/ቤተሰብ/ጎረቤት 88. ሌላ ካለ ይጠቀስ፡ ----------	
207.	**የመጀመርያውን ምልክት ከማየትዎ በፊት** በጡትዎ ውስጥ እጢ እንዳለ ለማወቅ እጅዎን ተጠቅመው እንዴት መዳሰስ እንዳለቦት ያውቁ ነበር?	0- አላውቅም 1- አዎ	
208.	**የመጀመርያውን ምልክት ከማየትዎ በፊት** ጡትዎን እጢ እንዳለው ለማወቅ በእጆ ተጠቅመው ይዳስሱት ነበር?	0- አልዳስስም ነበር 1- አዎ	
209.	**የመጀመርያውን ምልክት ከማየትዎ በፊት** ጡትዎን እጢ እንዳለው በሀኪም ምርመራ አድርገው ያውቃሉ?	0- አላውቅም 1- አዎ	
210.	**የመጀመርያውን ምልክት ከማየትዎ በፊት** ጡትዎን እጢ እንዳለበት በመሳርያ (ማሞግራም) የተደገፍ ምርመራ አድርገው ያውቃሉ?	0- አላውቅም 1- አዎ	
211.	ጡትዎ ላይ የጤና እክል እንዳለብዎ **ለመጀመሪያ ጊዜ** የተመለከቱት ወይም የተሰማዎት መቼ ነው?	----------/-------/----------**ቀን/ወር/አ.ም** (ቀን/ወር/አ.ም. ወይም ዓ.ም ብቻም ከሆነ በትክክል ይመዝገቡ።	ወሩን ና ዓ.ምን በትክክል ካስታወሱ ወደ ጥ.ቁ 213 ሂድ
212.	**ወሩን ካላስታወሱ** ነገር ግን አመተ ምህረቱን ካስታወሱ መጀመሪያ፣መሀል ወይስ መጨረሻ ነበር?	1. መጀመሪያ 2. መሀል 3. መጨረሻ 4. አላስታውሰውም	
213.	በመጀመሪያ ያዩት ምልክት ምን ነበር? **(ከአንድ በላይ መልስ ይቻላል)** **(ሁሉም ምርጫዎች ይነበቡ)**	1. የጡት ህመም 2. የጡት እብጠት 3. ከጡት ጫፍ የሚወጣ ፈሳሽ 4. የጡት ቆዳ መልክ መቀየር 88. ሌላ ይጠቀስ ----------	
214.	ለመጀመሪያው ጊዜ ምልክት ሲያዩ እርጉዝ ነበሩ?	0- አልነበርኩም 1- አዎ	
215.	ለመጀመሪያው ጊዜ ምልክት ሲያዩ ያጠቡ ነበሩ?	0- አላጠባም ነበር 1- አዎ	
216.	ለመጀመሪያው ጊዜ ምልክት ያገኘው ማን ነበር?	1. እራሴ 2. ባለቤቴ 3. ጤና ባለሙያ 88. ሌላ ይጠቀስ ----------	
217.	ለመጀመሪያው ጊዜ ምልክት ሲያዩ ምን ሊሆን ይችላል ብለው ነበር ያሰቡት?	1. ምች 2. እጢ 3. ካንሰር 4. ምንም	

		88. ሌላ ይጠቀስ ----------	
218.	ለመጀመሪያው ጊዜ ምልክት ሲያዩ ወድያውኑ የወሰዱት እርምጃ ምን ነበር?	1. ምንም አለደረኩም 2. ወድያውኑ ወደ ጤና ተቋም ሄደኩኝ 3. ወደ ባህል ሀኪም ሄድኩኝ 4. የሀይማኖት ስርዓት አከናወንኩኝ 88. ሌላ ይጠቀስ ----------	
219.	የጡት በሽታዎን ምልክቶችን ካዩ በኋላ ግን ህመምዎ ካንሰር መሆኑ ከመገለጡ በፊት የባህል ሀኪም ጋር ሄደው ነበር?	0- አዎ 1- አልሄድኩም 99- ለመመለስ አልፈልግም	**ወደ ጥ.ቁ. 221 ይሂዱ**
220.	መልሱ **አዎ ከሆነ፣** ምን አይነት የባህል ህክምና ነበር የወሰዱት?	_____ _____	
221.	የበሽታ ምልክቶችን ካዩ በኋላ ግን ህመምዎ ካንሰር መሆኑ ከመገለጡ በፊት ለመፍትሄ እንዲሆንዎ ያከናወንዎት ማንኛውም አይነት የሀይማኖት ስርአት ነበር?	0. አዎ 1. አልነበረም 99. ለመመለስ አልፈልግም	**ወደ ጥ. 223 ይሂዱ**
222.	መልስዎ **አዎ ከሆነ** ምን እንዳደረጉ ሊነግሩኝ ይችላሉ? **(ከአንድ በላይ መልስ ይቻላል) ምርጫዎቹን አንብብላቸው፣ ሌላ ካለም ጠይቃቸው**	1. ጸበል 2. ጸሎት 88. ሌላ ይገለጽ _____	
223.	ለመጀመሪያ ጊዜ በህመሞ ምልክቶች ምክንያት ወደ ጤና ተቋም የሄዱት መቼ ነበር?	----------/----------/--------- ቀን/ወር/አ.ም	**ወሩን ና ዓ.ምን በትክክል ካስታወሱ ወደ ጥ.ቁ 225 ሂድ**
224.	**ወሩን ካላስታወሱ** ነገር ግን አ.ም ካስታወሱ መጀመሪያ፣ መሀል፣ ወይስ መጨረሻ ነበር?	1. መጀመሪያ 2. መሀል 3. መጨረሻ 4. አላስታውሰውም	
225.	በመጀመርያ ወዴትኛው የጤና ተቋም ነበር የሄዱት?	1. ጤና ጣቢያ 2. የመንግስት ሆስፒታል 3. የግል ሆሰፒታል 4. የግል ክሊኒክ	
226.	ወደ ጤና ባለሙያ ከመሄድዎ በፊት መጀመርያ ካዩት ተጨማሪ ሌሎች ምልክቶችን አይተው ነበር?	0- አላየሁም 1- አዎ	**ወደ ጥ. 228 ይሂዱ**
227.	መልሱ አዎ ከሆነ ተጨማሪ ምልክቶቹ ምን ነበሩ? **(ከአንድ በላይ መልስ ይቻላል) (ሁሉም ምርጫዎች ይነበቡ)**	1. ህመም 2. እብጠት 3. የማሳከክ/ማቃጠል ስሜት 4. ከጡት የሚወጣ ፈሳሽ 88. ሌላ ካለ ይገለጽ፡ ----------	
228.	የጤና ባለሙያ እንዲያይዎት ያነሳሳዎት ዋናው፡ ነገር ምንድን ነበር?	1. በመጀመርያው ምልክት 2. ተጨማሪ ምልክቶች 3. የቤተሰብ አባል ግፊት	

		4. የጓደኛ ግፊት 5. ለሌላ ህክምና በሄድኩበት ጊዜ ጤና ባለሙያው ጡቴን መርምሮኝ 88. ሌላ ካለ ጥቀስ ----------	
229.	ለመጀመሪያ ጊዜ በሽታዎን ለመለየት የናሙና ውጤት የተገለፀበት ቀን መቼ ነው? **(እባክዎን የናሙና ውጤት ኣይተው በትክክል ቀኑን ይጻፉ)**	------/-------/----------ቀን/ወር/አ.ም	
230.	የገጠሞት የጡትዎን የጤና እክል ለማረጋገጥ **ናሙና እስከተወሰደበት ግዜ** ድረስ ምን ያህል ጤና ተቋም ሄደዋል?	_____**የ**ጤና ተቋም ብዛት	
231.	የገጠሞት የጡትዎን የጤና እክል ለማረጋገጥ **ናሙና እስከተወሰደበት ግዜ** ድረስ ምን ያህል ግዜ ወደ ጤና ተቋም ተመላልሰዋል?	_____ጊዜ	
	<u>ማብራርያ</u> እባክዎን የጥያቄ ቁጥር 211 ና 223 መልስ በመመልከት ከ3 ወር በላይ መቆየታቸው ያረጋግጡ። የህመምዎን የመጀመርያ ምልክት ካዮበት ቀን እስከ የመጀመርያ ህክምና ያደረጉበት ቀን 3 ወርና ከዛ በላይ ለዘገዩ ሴቶች የሚከተሉትን ጥያቄ ቁጥር 232 ና 233 ጠይቅ።		
232.	ወደ ህክምና ቶሎ እንዳይሄዱ ያደረጎዎት ዋነኛው ምክንያት ምንድ ነበር?	_____ _____	
233.	ቀጥሎ ከማነብልዎት አማራጮች መካከል በቶሎ ወደ ህክምና እንዳይሄዱ ምክንያት የሆኑብዎት የትኞቹ ነበሩ? (ሁሉም ምርጫዎች ይነበቡ) **(መልስ ሊሆን የሚችሉትን ሁሉ ያክብቡ)**	1. መጀመሪያ በነበረው ችግር አልተጨነኩም ነበር 2. ቤት ውስጥ በነበረኝ ሀላፊነት ወይም በስራዬ ምክንያት ጊዜ አልነበረኝም 3. በሀኪም ወይም በሌላ የጤና ባለሙያ ለመመርመር ፈረቼ ነበር 4. የምርመራውን ውጤት ፈርቼ ነው 5. ሕክምናውን ፈርቼው ነበር 6. የባህል ሀኪም መጀመሪያ አይቶኝ ነበር 7. ትክክለኛ የጤና ተቋም የት እንደሆነ አላውቅም ነበር 8. ማንኛውም ሰው ስለ ችግሬ እንድያውቅ አልፈልግም ነበር። 9. ህክምናው በጣም ውድ ነው ብዬ አስቤ ነበር። 88. ሌላ ካለ ጥቀስ----------	

ክፍል 2፡ የጡት ካንሰር መጠይቅ ሁለት

የጡት ካንሰር ታካሚዎች መጠይቅ II

የመጠይቅ ቁጥር፡ _____ የቃለ መጠይቅ ቀን_____/_____/_____

የታካሚዋ የሕክምና መዝገብ ቁጥር_____

የተሳታፊዋ ስልክ ቁጥር:_____

የተሳታፊዋ የቅርብ ዘመድ ስልክ ቁጥር:_____ዝምድና:_____

ቃለ መጠይቅ አድራጊው ስም፡ ዶ/ር/ወ/ሮ፣ወ/ት_____ቀን:__/___ / _____

የአስተባባሪ ስም፡ ወ/ት: _____ ፊርማ: _____ ቀን: ___ / ___ /____

2. 1. የጡት ካንሰር ታካሚዎች የህክምና ሁኔታ

ተ.ቁ	መግለጫ	ምርጫዎች	ወደ ጥ. ቁጥር
201.	ለካንሰሩ የወሰዱት ህክምና አለ?	0. የለም → 1. አለ	ጥ 204
202.	መልሱ አዎን ከሆነ፣ ምን አይነት ህክምና ነው የወሰዱት? (ከአንድ በላይ መልሶች መመለስ ይቻላል)	1. ካንሰሩን ለማስወገድ የቀዶ ጥገና ህክምና 2. ኬሞቴራፒ 3. የጨረር ሕክምና 4. የሆርሞን ሕክምና 88. ሌላ ካለ ይገለጽ _____	
203.	እባክዎን ሕክምና የወሰዱበት ጤና ተቋም ይንገሩን?	_____	
204.	በሽታዎትን ካወቁ በኋላ የፈለጉትን ሕክምና እንዳይወስዱ ችግር የሆነብዎት ማናቸውም ችግር ነበር?	0. አልነበረም → 1. ነበር	ጥ 206
205.	ህክምናውን እንዳያገኙ ያደረግዎት ዋና ምክንያት ምን ነበር? **ከአንድ በላይ መልስ መስጠት ይቻላል**	1. የሕክምናውን ወጪ የመክፈል አቅም አልነበረኝም 2. ሕክምናው ሀገር ውስጥ የሚገኝ አልነበረም 3. ሕክምናውን ለማገኘት ብዙ ጊዜ ይወስድ ነበር 4. ለሕክምናው ቀጠሮ ለማስያዝ ከባድ ነበር 5. ሐኪሞችን ማመን/ በሐኪሞች መተማመን አልቻልኩም ነበር 6. ኢንሹራንሴ የሕክምና ወጪዬን አይሸፍንም ነበር 7. ለሕክምና የት መሄድ እንዳለብኝ አላወኩም ነበር 88. ሌላ ካለ ይገለጽ_____	

2.2. በሽታውን ካወቁ በኋላ የካንሰር ሕክምና ለማግኘት የባሕል ሐኪም ጋር የሄዱ ታካሚዎች

ተ.ቁ	ጥያቄዎች	ምርጫዎች	ወደ ጥ. ቁጥር

206.	ከሐኪምዎት ውጪ የባሕል ሐኪም ጋር ሄደው ያውቃሉ?	0. አላውቅም → **ጥ 301** 1. አውቃለሁ	
207.	መልስዎ አዎን ከሆነ፣ ምን አይነት የባህል ሐኪም ነበር የሄዱት?	1. መድሃኒት ቀማሚ ጋር 2. መንፈሳዊ ሀክምና (Spiritual healer) 88. ሌላ ካለ ይገለጽ _____	
208.	ይህንን ሕክምና የተጠቀሙት ዋና ምክንያት ምን ነበር? **ከአንድ በላይ መልስ መስጠት ይቻላል**	1. ካንሰሬን ለማከም 2. የካንሰር ሕክምናውን የጎንዮሽ ችግሮች ለመቀነስ 3. በካንሰሩ ምክንት የሚሰማኝን ሕመም ለማስታገስ 4. ከጭንቀቴ ለመዳን 88. ሌላ ምክንያት ካለ ይገለጽ _____	

2.3. ስለ ኬሞቴራፒና ሆርሞን ሕክምና የተሳታፊዎች አመለካከት

ተ.ቁ	ጥያቄዎች	ምርጫዎች	ወደ ጥ. ቁጥር
301.	ኬሞቴራፒ ወስደዋል?	0. አልወሰድኩም → ጥ 305 1. ወስጃለሁ	
302.	መልስዎ አዎን ከሆነ፣ ሀኪምዎ ለምን ያህል ዙር አዞልዎታል?	_____ ቁጥር 99. አላውቀውም	
303.	የታዘዝልዎትን ሁሉንም ዙር ወሰደው ጨርሰዋል?	0. አልጨረስኩም 1. ጨርሻለሁ → ጥ 305	
304.	መልስዎ **አልጨረስኩም** ከሆነ ዋናው ምክንያት ምንድን ነበር?	1. የህክምናውን ቀጠሮ አልጠበኩም ነበር 2. የጎንዮሽ ጉዳቶቹን መቋቋም አልቻልኩም ነበር 3. ለህክምናው መክፈል አቅም አልነበረኝም 4. የመድኀኒቱን ፈዋሽነት አላመንኩበትም ነበር 5. መድኀኒቱ አለተገኘም ነበር 88. ሌላ ካለ ይገለጽ _____	
305.	የሆርሞን ህክምና እየወሰዱ ነው?	0. አይደለም → መጠይቁን ያልቃል 1. አዎን፣ እየወሰድኩ ነው	
306.	የታዘዘልዎትን የሆርሞን ህክምና ሳይወስዱ የቀሩበት አጋጣሚ ነበር?	0. አልነበረም → መጠይቁን ያልቃል 1. አዎን፣ ነበር	
307.	መልስዎ አዎን ከሆነ፣ ምን ያህል ጊዜ	_____ ጊዜ	

	ሳይወስዱ ቀሩ?		
308.	መድኃኒቱን ያልወሰዱበት ምክንያት ምን ነበር?	1. የመድኃኒቱ የጎንዮሽ ችግር 2. የገንዘብ ችግር 3. የመድኃኒቱ አለመኖር 4. ለመውሰድ ረስቼ ነበር 88. ሌላ ካለ ይገለጽ _____	

ከካንሰር ሕመምዎ ጋር ተያይዞ ሊነግሩኝ የሚፈልጉት ማናቸውም ነገር ካለ እባክዎትን ይንገሩኝ

_____

በዚህ ጠቃሚ ጥናት ላይ ተሳታፊ ስለሆኑ አመሰግናለሁ!

Annex VI: Amharic version in-depth interview guides

ክፍል-1፡ <u>በቃለ-መጠይቁ ለሚሳተፉ የተዘጋጀ የስምምነት ውል ቅፅ</u>

መግቢያ

ሊያነጋግሩኝ ፍቃደኛ ስለሆኑ በጣም አመሰግናነሁ። ስሜ _____ ሲሆን፣ በአዲሰ አባባ ዩኒቨርስቲ፣ በሕ/ሰብ ጤና አጠባበቅ ትምህረት ክፍል ነው የምሰራው፣ የመጣሁት ደሞ የጡት ካንሰር፣ ቤተሰብ እና ጤና ባለሙያ ለማነጋገር ነው። የጡት ካንሰር በአፍሪካ እነዲሁም በሃገራችን ዋና የእናቶች በሽታ ና ለሞመት ከሚዳረጉት በሽታዎች በቁጥር አንድ የሚግኝ በሽታ ነው። በአሁኑ ሰዓት በሴቶች ላይ ከሚከሰቱ የካንሰር በሽታወች በአንደኛ ና ለሞት በመዳረግ በሁለተኛ ደረጃ ይገኛል። ዋነኛው መከላከልያው መንገድ ደግሞ የቅድመ ካንሰር የጡት ምርመራ ማድረግ ና ምልክት ሲታይ ኣሰፈላጊውን የህክምና ክትትል ማድረግ ነው።

<u>የጥናቱ ዓላማ:</u> ከቅርብ ጊዜ ወዲህ የጡት ካንሰር በሀገራችን ዋነኛው የእናቶች የመታመም እና መሞት መንሲኤ ሆኖ ሳለ፤ የቅድመ ካንሰር የጡት ምርመራ ናየበሽታው ምልክት ሲታይባቸው ቶሎ ወደ ህክምና መምጣት ሁኔታ ዝቅተኛ ሊባል የችላል። አበዛኛቹ እናቶች ወደ ህክምና ሚመጡት በሽታው ከጡት አልፎ ወደ ሌላ ሰውነት ኣካላቸው ከተሰራጨ በኃላ ነው። ይህ ሆኖ ሳለ ስለችግሩ መንስኤ በኢትዮጵያ የሚታወቀው በጣም ጥቂት ብቻ ነው። በመሆኑም በዚህ ጥናት የናንተ ተመኩሮ ማለትም በሽታው ካያቹሁበት ቀን እስከ ኣሁን ድረስ እንዴት እንደነበረ ለመማርና እናቶች ዘግይተው የሚመረመሩበት ምክንያት ለማወቅ ነው። ምክንያቶችኝ ለይቶ ማወቅ እናቶች የጡት ጫፍ ካንሰር ምርመራ እንድያደርጉ ና ምልክት ሲያዩ ቶሎ ሃኪም እንድያማክሩ ለሚደረጉ ስራዎች ጠቃሚ ነው።
<u>ተሳትፎ፡-</u> እርሶና ሌሎችን በፍቃደኝነት ላይ የተመሰረተ ተሳትፎ እንዲያደርጉ እንጠይቆታለን።

<u>ተጋላጭነት፡-</u> ጥናቱ በምንም መልኩ የጥናቱን ተሳታፊ ተጋላጭ አያደርገውም። እንዲሁም መጠይቁ ለብቻ ለዚህ መጠይቅ ተብሎ በተዘጋጀ ቢሮ የሚደረግ ነው። ጥናታችን በመጠይቅ ላይ ብቻ መሰረት ያደረገ ሲሆን ምንም አይነት ምርመራን የሚጠየቅ ነገር የለውም።

<u>ከጥናቱ የሚገኘው ጥቅም፡-</u> ለእርስዎ ቀጥታዊ የሆነ ጥቅም ባይኖረውም፣ የእርስዎን በጥናቱ ተሳታፊ መሆን በጥናቱ ላይ የተጠቀሱትን ጥያቄዎች ለመመለስና ለወደፊት የሕብረተሰቡ በተለይም የሴቶች ጤና መሻሻል ከፍተኛ አስተዋፅዖ ያደርጋል።

<u>ሚስጥራዊነት</u>፡- በጥናቱ ወቅት ስለ እርስዎ የምንሰበስበው ማንኛውም መረጃ ሚስጥራዊነቱ የተጠበቀ ነው። እርስዎን የሚገልጽ መረጃ ሌላ መለያ ቁጥር ከተሰጠው በኃላ ለብቻው ማንም እንዳያገኘው ሆኖ ይቀመጣል። የጥናቱ ዋና ተመራማሪዎች ብቻ እርስዎን በህክመናው እንዲረዱ የሚያስፈልግ ነው ብለው ካመኑ፣ የተሰጠውን መለያ ቁጥር የእርስዎን ማንነት ለመለየት ሊጠቀሙበት ይችላሉ። ነገር ግን የእርስዎን ማንነት ሳይገለጥ ከህክምናው ጋር ተያይዞ ያሉ መረጃዎች በተመራማሪዎች እንዲሁም ከአስፈለገ በስነ-ምግባር ኮሚቴ ሊታይ ይችላል።

<u>ያለመሣታፍ ወይም ከጥናቱ የማቋረጥ መብት፡</u> በዚህ ጥናት መሳተፍ ካልፈለጉ ያለመሳተፍ ሙሉ መብት አለዎት። እንዲሁም ያለመሳተፍዎ በዚህ ሆስፒታል በሚያገኙት ሕክምና ላይ ምንም አይነት ተጽኖ አያሳድርም። በዚህ ሆስፒታል የሚያገኙት ማንኛውም ጥቅም እንደተጠበቀ ይሆናል። እንዲሁም ጥናቱ ላይ መሳተፍ ከጀመሩ በኃላ በማንኛውም ጊዜ እንደታካሚ በዚህ ሆስፒታል ያለዎትን መብት ሳያጡ የማቋረጥ መብትዎን የተጠበቐ ነው። በማንኛውም ሁኔታ በዚሕ ክሊኒክ ውስጥ የሚያገኙት ህክምና በዚህ ጥናት ውስጥ በመሳተፍዎ ወይም ባለመሳተፍዎን የሚቀየር ነገር አይኖረውም።

<u>ግፊት፣ ማበረታቻ፣ካሳ፡</u> ይህ ጥናት ተሳታፊው ላይ የሚያሳድረው ምንም አይነት ተጽኖም ይሁን ግፊት ይሁን በጥናቱ እንዲሳተፉ የሚሰጥ ማበረታቻ የለውም። ጥናቱ ለካሳ መስጠት ያሚደርስ ምንም ጉዳት የለውም።

<u>የጥናቱ ውጤት ስርጭት፡</u> ተመራማሪው የጥናቱን ውጤት በተለያዩ ማሰራጫ መንገዶች፣ በሰሚናር፣ ኮንፈረንስ የማሰራጨት ሀላፍነት አለው። እንዲሁም የጥናቱ ውጤቶች በአለም ኣቀፍ የምርምር መጂሄቶች እንዲታተሙ ይደረጋል።

<u>ስለ ጥናቱ ተጨማሪ መረጃ ከፈልጉ፡-</u> ማንኛውም ጥያቄ ካሎት ከዚህ በታች የተጠቀሱትን ሰዎች ማነጋገር ይችላሉ። በማንኛውም ጊዜ ልታነጋግሩዋቸው ትችላላችሁ። በኋላም ላይ ማንኛውም ጥያቄ ካለችሁ፣ የጥናቱን ተመራማሪዎች ከታች በተጠቀሱት አድራሻዎች ማግኘት ይችላሉ።

አቶ አለም ገ/ማርያም (ስልክ ቁ.፡ 0910-35-29-15- ኢ-ሜል- alemg25@gmail.com)
ፕሮፌሰር አለማየሁ ወርቁ (ስልክ ቁ.፡ +251-11-551-37 15; ኢ-ሜል alemayehuwy@yahoo.com)
ዶር. አዳሙ አዲሴ (ስልክ ቁ.፡ +251-11-55-47319; ኢ-ሜል: adamuaddissie@gmail.com)

የተቋሙ፡ ጥናቱን፡ የሚመለከት፡ ኮሚቴ
አድራሻ፡ አዲስ አበባ ዩንቨርስቲ የጤና ሳይንስ ኮሌጅ
ስልክ፡ +251- 118-96-13-96

<u>ክፍል 2፡ የስምምነት ውል ቅጽ</u>
እኔ ከዚህ በታች ስሜ የተገለጸው የዚህን ጥናትን አላማ በመገንዘብ እንዲሁም ሀሳቤን ከቀየርኩ የመውጣት መብት እንዳለኝ በማወቅ በዚህ ጥናት ለመሳተፍ መስማማቴን አረጋግጣለሁ።
እኔ _____ ለወ/ሮ/ለወ/ሪት/ሲ/ር _____ በዚህ ጥናት ለመሳተፍ መስማማቴን እገልጻለሁ። ስለጥናቱ አስፈላጊው መረጃ ተሰቶኛል። እንዲሁም በፈለኩት ጊዜ ካለ ምንም ቅደመ ሁኔታ ወይም የማገኘው የህክምና ድጋፍ ላይ ተጽኖ ሣያሳደር ከጥናቱ ማቋረጥ እንደምችል ተረጋግጦልኛል። በሚገባኝ ቋንቋ ስለ ጥናቱ መግለጫ ተደርጎልኛል።

በጥናቱ ለመሳተፍ ፍቃደኛ ኖት?
አዎ ☐ አይደለሁም ☐ **(አይደለሁም ካሉ ኣመስግነው ቃለ-መጠይቁን እዚህ ላይ ያቁሙ)**

የተሳታፊ ፊርማ፡ _____

ቃለ-መጠየቁን ያደረገው ሰው ስም፡ ወ/ሮ/ወ/ሪት/ሲ/ር _____ቀን___/___/___

ለመሳተፍ ፍቃደኛ ስለሆኑ በጣም አመሰግኖታለሁኝ።

ቃለ-መጠይቁ ለመጨረሽ እሰከ አንድ ሰዓት ሊወስድብን ይችላል። እሚሰጡኝን አሳብ ሆነ አስታየት በሙሉ ለመያዝ እንዲጠቅመኝ፣ ፍቃድዎን ከሆነ የድምጽ መቅጃ ልጠቀም ነው። በውይይታችን ግዜ ዋና ዋና የውይይቱን ነጥቦችን ብይዝም እንኳ እሚነግሩኝን ሀሳብ በሙሉ በመጻፍ ሊይዘው ሊከብደኝ ና ላልፈጥን እችላለሁኝ። እባክዎን ድምጽዎን በደንብ እንዲቀዳ ና ባኋላ አዳሚጨ ለመጻፍ እንዳያስቸግረኝ፣ ጠራ ብለው ያዋሩኝ። በድጋሜ እሚሰጡኝን ሀሳብ ሚስጠሩን የተጠበቀ መሆኑን ላረጋግጥሎት እወዳለሁኝ። እሚሰጡኝን ሀሳብ ከሌሎች ተሳታፊዎች ከሚገኘው ሀሳብ ተጠናቅሮ እንደሚቅርብ ሲገልጽ፤ ሲቀርብ ደግሞ የእርስዎን ሆነ የሌሎች ተሳታፊዎች መንነት በማይገልጽ ሁኔታ እንደሆነ ላረጋግጥሎት እወዳለሁኝ።

መጠይቃችን ከመጀመራችን በፊት፣ ሊጠይቁት የሚፈልጉት ነገር ካለ?

የተሳታፊዎች አድራሻ

መጠይቅ፡ ቁጥር፡ _____

የተሳታፊ የህክምና መዝገብ ቁጥር፡ _____

የጤና ተቋሙ ስም፡_____

<u>የተሳታፊዎች አድራሻ:</u>

ክ/ከተማ:_____ወረዳ :____ቀበሌ:_____የቤት ቁጥር፡ _____

የተሳታፊ ሞባይል ቁጥር:_____

የተሳታፊዎች ስነ-ህዘባዎ ሁኔታ

እድሜ**:** _____
የትዳር ሁኔታ: ___
የትምህርት ደረጃ: _____
የሚሰሩት የስራ መደብ**:** _____

ክፍል 3፡ ጡት ካንሰር ካለባቸው እናቶች ጋር የሚደረግ-ቃለ-መጠይቁን መመርያ

1. በአከባቢዎን ስለ የጡት ካንሰር ምን ይታወቃል?
    - የጡት ካንሰር መንሴው
    - ምልክቱ
    - ቅድመ ምርመራ
    - ህክምናው
    - እገዛ
2. የህመምዎን ምልክት ከማየትዎ በፊት ስለጡት ካንሰር ሰምተው ያወቃሉ?
    - መቼ፣ እንዳት ነበር የሰሙት
3. የጡት ካንሰር ምልክት ካዩበት ቀን ጀምሮ እስከ ካንሰር መሆኑን የተረጋገጠበት ግዜ የነበሮት ተመክሮ ሊነግሩኝ ይችላሉ?
    - የጡትዎን ህመም/ችግር መጀመርያ ያገኘው ማን ነበር?
    - እንዴት ነበር መጀመርያ የጡትዎን ችግር ያገኙት?
    - መጀመርያ ምልክት ባዩት ግዜ ምን ተሰማዎት?
    - ህመሙን ከተሰማቦት በኋላ ምን ምን እርመጃዎች ወሰዱ?
    - መች ነበር ወደ ህክምና የሄዱት?
    - ለምን ወደ ህክምና እንዲሄዱ ቢነግሩኝ (የበሽታው ምልክት/ የምልክቱና ህመሙ መጨመር)
    - ህክምና እዲሄዱ ያገዞት/ የገፋፉዎት ሰው ነበረ?
    - በሽታዎን ካንሰር መሆኑ የተረጋገጠው መች ነበር?
    - ህመሙ ከተሰማዎት ቀን ጀምሮ የወሰዱት/የሞኮሩት መፍትሄ ምን ነበር (ከመረጋገጡ በፊት እና በኋላ)
    - ህመምዎን ካንሰር መሆኑን ያረጋገጦሎትን ማን ነበር?
    - ህመምዎን ካንሰር መሁኑን በሚረጋገጥበት ግዜ የነበረው ደረጃ?
    - ህመምዎን ካንሰር መሆኑን ለማረጋገጥ ባደረጉት ምርመራ የረዳዎትን ነገር ይነገሩኝ?
4. በሽታዎን ካንሰር መሆኑን እስከ ተረጋገጠበት ግዜ ያጋጠሞት ተግዳሮቶች ሊነግሩኝ ይችላሉ?
5. እናቶች ምልክት ካዩ ወደ ህክምና ለምን ቶሎ እንደማይመጡ ሊነግሩኝ ይችላሉ? (እንቅፋቶች ምንድን ናቸው)
    - የእናቶች ኢኮኖሚ ና ማህበረሰባዊ ሁኔታ (እድሜ፣ ትምህርት ደረጃ፣ ገቢ)
    - ግለሰባዊ ምክንያቶች (ወደየት እንደሚሄዱ አለማወቅ፣ ትኩረት አለመስጠት፣ ፍራቻ፣ የገቢ እጥረት፣ የበሽታውን ምልክት አቅልሎ ማየት)
    - ከባህል ጋር የተያያዘ ምክንያት (ባህላዊ ህክምና፣ የህ/ሰብ እምነት)
    - የህክምና አገልግሎት ስርዓት ጋር የተያያዘ ምክንያት (ቀረቤታ፣ ሪፈራል)
6. እናቶች ምልክት ካዩ በኋላ ቶሎ ወደ ህክምና እንዲመጡ ና ጤና ተቋሙም የበሽታው ዓይነት ቶሎ እንዲለይ እንደመፍትሄ ምን ቢደረግ ይላሉ?
    - በግለሰብ ደረጃ መደረግ ያለበት
    - በህ/ሰብ ደረጃ መደረግ ያለበት
    - በጤና ተቋም መደረግ ያለበት
    - በመንግስት ደረጃ መደረግ ያለበት
    - ለእናቶች የጡት ካንሰር ቅድመ ምርመራ በተመለከተ ምን ትመክርያቸዋለሽ?
7. ተጨማሪ ሊነግሩኝ ወይም ሊጠይቁኝ የሚፈልጉት ነግር ካሎት እባክዎት?

ለሰጡኝ ጠቃሚ መረጃ እጅግ በጣም አድሪጌ አመሰግኖታለሁኝ!!

ክፍል 3፡ ከጡት ካንሰር ታማሚ ቤተሰብ ጋር የሚደረግ-ቃለ-መጠይቁን መመርያ

1. ስለእርስዎን ሊነግሩኝ ይችላሉ?
2. ከታማሚዋን ሎት ዝምድና ምንድን ነው?
3. ስለ ካንሰር መወያት እንችላለን?
    - ስለ ካንሰር ምን ያውቃሉ?
    - ሰዎች ካንሰር ምንድን ነው ብለው ያስባሉ?
    - የጡት ካንሰርስ?
    - በአከባቢዎን የጡት ካንሰር መጠርያ ካለው ይንገሩኝ
    - በአከባቢዎን ስለ የጡት ካንሰር ምን ይታወቃል? (መንሴው፣ ሀክምናው፣ መዳን)

1. ስለ ዘመድዎን (የታማሚን ስም) ሊነግሩኝ ይችላሉ?
2. በመጀመርያ ግዜ የዘመድዎን ህምም የጡት ካንሰር መሆኑን ሲታወቅ፣ ዘመድዎ (የታማሚን ስም) እን እርስዎ ምን ተሰማችሁ?
    - ህመምዎን ካንሰር መሆኑን ያረጋገጡሎትን ማን ነበር?
    - በዛኔ የዘመድዎን ስሜት እንዳት ነበር?
3. ዘመድዎን (ስምዋን) ስለ ካንሰር ህመምዎን ምን እንደተሰማዎት ሊነግሩኝ ይችላሉ?
    - ተስፋ የመቁረጥ
    - የመገለል ፍራቻ፣ የግበረ-ስጋ ግንኙነት
    - በትዳር ላይ ሊያከትል የሚችለው ችግር ፍራቻ
    - ስለ ካንሰር ከታማሚዋን ለማውራት ምን ያህል ቀላል ነው?
4. የዘመድዎን በሽታ ካንሰር መሆኑን እስከ ተረጋገጠበት ግዜ ያጋጠሞት ዋና ዋና ተግዳሮቶች ሊነግሩኝ ይችላሉ?
8. እናቶች ምልክት ካዩ ወደ ህክምና ለምን ቶሎ እንደማይመጡ ሊነግሩኝ ይችላሉ? (እንቅፋቶች ምንድን ናቸው)
    - የእናቶች ኢኮኖሚ ና ማህበረሰባዊ ሁኔታ (እድሜ፣ ትምህርት ደረጃ፣ ገቢ)
    - ግለሰባዊ ምክንያቶች (ወደየት እንደሚሄዱ አለማወቅ፣ ትኩረት አለመስጠት፣ ፍራቻ፣ የገቢ እጥረት፣ የበሽታውን ምልክት አቅልሎ ማየት)
    - ከባህል ጋር የተያያዘ ምክንያት (ባህላዊ ህክምና፣ የህ/ሰብ እምነት)
    - የህክምና አገልግሎት ስርዓት ጋር የተያያዘ ምክንያት (ቀረቤታ፣ ሪፈራል)
9. እናቶች ምልክት ካዩ በኋላ ቶሎ ወደ ህክምና እንዲመጡ ና ጤና ተቋሙም የበሽታው ዓይነት ቶሎ እንዲለይ እንደመፍትሄ ምን ቢደረግ ይላሉ?
    - በግለሰብ ደረጃ መደረግ ያለበት
    - በህ/ሰብ ደረጃ መደረግ ያለበት
    - በጤና ተቋም መደረግ ያለበት
    - በመንግስት ደረጃ መደረግ ያለበት
10. ተጨማሪ ሊነግሩኝ ወይም ሊጠይቁኝ የሚፈልጉት ነግር ካሎት እባክዎት?

ለሰጡኝ ጠቃሚ መረጃ እጅግ በጣም አድሪጌ አመሰግኖታለሁኝ!!

ክፍል 4፡ ከጤና ባለሙያ ጋር የሚደረግ-ቃለ-መጠይቁን መመርያ

1. ቃለ-መጠይቃችን ከመጀመራችን በፊት፣ ስለእርስዎን ሊነግሩኝ ይችላሉ?
    - የትምህርት ደረጃ፣ የአገልግሎት ዘመን፣ የስራ ክፍል
2. የካንሰር ታማሚን ማከም ወይም መንከባከብ ከጀመሩ ምን ያህል ግዜ ሆኖታል ?
    - በብዛት የሚያክሙት/የሚንከባከቡት የካንሰር አይነት ምንድን ነው?
    - በዚህ ክፍል ዋና የስራ ድርሻዎ ምንድን ነው?
3. ስለ ካንሰር ማውራት እንችላለን?
    - ስለ ካንሰር ምን ያውቃሉ?
    - ሰዎች ካንሰርን እንዴት ይገልጹታል?
    - የጡት ካንሰርስ?
    - የአከባብያዊ ስያሜ/ስም ካለው ሊነግሩኝ ይችላሉ?
    - ሕብረተሰቡ በጡት ካንሰር ያለው ምልከታ እንዴት ይገልጹታል? (መንሴው፣ ህክምናው፣ መዳን መቻል)
4. የካንሰር ታማሚዎች ካንሰርን እንዴት ይገልጹታል?
    - ካንሰር እንደታመሙ እንዴት ነው የሚነገራቸው?
    - ቀድማቹ ውጤቱን ለማን ነው የምትነግሩት?
    - ስለ ካንሰር ከታማሚዋን ለማውራት ምን ያህል ቀላል ነው?
    - ታማሚዎችን ተስፋ ከመቁረጥ፣ የመገለል ስማት/ፍራቻ፣ ግብረ-ስጋ ግንኙንት እንዴት ታያቸዋለህ/ሽስለ ካንሰር ከታማሚዋን ለማውራት ምን ያህል ቀላል ነው?
5. የታማሚዎን ህመም ካንሰር መሆኑን ከመግለጽ ጋር ጠተያይዞ ነገር ካለ ሊነግሩን ይችላሉ?
6. የጡት ካንሰር ቶሎ እንዳይታወቅ/እንዳይለይ ከሚያደርጉ ተግዳሮች ይንገሩኝ
7. ተጨማሪ ሊነግሩኝ ወይም ሊጠይቁኝ የሚፈልጉት ነግር ካሎት እባክዎት?

ለሰጡኝ ጠቃሚ መረጃ እጅግ በጣም አድሪጌ አመሰግኖታለሁኝ!!

Annex VII: Original papers and manuscripts

Anex VIII. Declaration

I, the undersigned, declare that this is my original work, has never been presented in this or any other University, and that all the resources and materials used for the dissertation, have been fully acknowledged.

Name: Alem Gebremariam Abraha

Signature: _____

Date: May 18, 2021____

Place: Addis Ababa, Ethiopia

Date of Examination: May 18, 2021

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

Name: Prof. Alemayehu Worku (PhD)

Signature: _____

Date: _____

BMJ Open

Time intervals experienced between first symptom recognition and pathologic diagnosis of breast cancer in Addis Ababa, Ethiopia: a cross-sectional study

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ABSTRACT

Objectives This study aimed to estimate the magnitude of patient and diagnostic delays and associated factors among women with breast cancer in Addis Ababa.

Design This is a cross-sectional study.

Settings and participants All women newly diagnosed with breast cancer in seven major healthcare facilities in Addis Ababa (n=441) were included in the study.

Main outcomes and measures Patient interval (time from recognition of first symptom to medical consultation) and diagnostic interval (time from first consultation to diagnosis). Patient intervals >90 days and diagnostic intervals >30 days were considered delays, and associated factors were determined using multivariable Poisson regressions with robust variance.

Results Thirty-six percent (95% CI [31.1%, 40.3%]) of the patients had patient intervals of >90 days, and 69% (95% CI [64.6%, 73.3%]) of the patients had diagnostic intervals of >30 days. Diagnostic interval exceeded 1 year for 18% of patients. Ninety-five percent of the patients detected the first symptoms of breast cancer by themselves, with breast lump (78.0%) as the most common first symptom. Only 8.0% were concerned about cancer initially, with most attributing their symptoms to other factors. In the multivariable analysis, using traditional medicine before consultation was significantly associated with increased prevalence of patient delay (adjusted prevalence ratio (PR) = 2.13, 95% CI [1.68, 2.71]). First consultation at health centres (adjusted PR = 1.19, 95% CI [1.02, 1.39]) and visiting ≥4 facilities (adjusted PR = 1.24, 95% CI [1.10, 1.40]) were associated with higher prevalence of diagnostic delay. However, progression of symptoms before consultation (adjusted PR = 0.73, 95% CI [0.60, 0.90]) was associated with decreased prevalence of diagnostic delay.

Conclusions Patients with breast cancer in Addis Ababa have prolonged patient and diagnostic intervals. These underscore the need for public health programme to increase knowledge about breast cancer symptoms and the importance of early presentation and early diagnosis among the general public and healthcare providers.

Strengths and limitations of this study

- It is the first multicentre study on the extent of patient and diagnostic delays of breast cancer and associated factors in Ethiopia with incident breast cancer cases recruited from seven major health facilities in Addis Ababa city, representing 90% of all breast cancer cases in the city and making the findings more generalisable.
- It is also the first study to examine the extent of patient and diagnostic delays and associated factors using primary data obtained from incident cases of breast cancer.
- The retrospective nature of collecting information about dates of symptom recognition and medical consultations is prone to recall bias.
- The interviews were conducted in a hospital setting, which could have resulted in a social desirability bias leading to under-reporting of time interval before medical consultation and over-reporting of desirable behaviour such as self-breast examination.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women in Ethiopia, as in other parts of Africa.[1–4] In Addis Ababa, the capital city of Ethiopia, breast cancer accounts for one-third of all female cancers.[1] The burden of this disease is increasing in the city[1 5] in part because of rapidly changing reproductive patterns[6]: average age at first birth is rising, and the fertility rate is dropping. Similar to other areas in sub-Saharan Africa,[7] a substantial proportion of patients with breast cancer in Addis Ababa are diagnosed at a late stage of the disease[8] when treatment options are limited[9 10] and the chance of survival is poor.[8 11]

The reasons for late-stage diagnosis may include prolonged patient interval (time interval in seeking medical care after recognition of symptoms) and diagnostic interval (time intervals between initial medical consultation and diagnostic confirmation).[7 12 13] Waiting >3 months before seeking care after recognition of symptoms has been associated

with advanced-stage disease[7] and poorer survival.[14] Similarly, prolonged diagnostic interval has been associated with lower survival.[15] Thus, understanding patients' pathways to diagnosis and the duration of these time intervals is important to developing interventions to promote earlier detection.

Only two previous studies have documented patient interval (symptom duration) of breast cancer among women in Ethiopia.[16 17] One of these studies was conducted 10 years ago and was based on 69 patients diagnosed from 2003 to 2007 in a referral hospital,[16] while the second study was a retrospective study based on 404 patients treated from 1 October 2005 to 30 September 2015 in one private clinic.[17] Thus, the findings from these studies may not reflect the current time interval patterns in Addis Ababa or nationwide. In this analysis, we investigated time intervals experienced by women with breast cancer, from recognition of symptoms to pathological diagnosis of the disease. We also examined factors associated with patient and diagnostic intervals >90 days and >30 days, respectively. The findings from this study could inform public policy interventions aimed at decreasing stage at diagnosis and thereby improving survival.

METHODS

This paper is part of an ongoing broader project described in detail in the published protocol.[18] Briefly, the methods are summarised as follows.

Study design and sample size

A cross-sectional study was conducted based on data drawn from an ongoing follow-up study in Addis Ababa.[18] A baseline survey was conducted among a cohort of 441 newly diagnosed female patients with breast cancer ages ≥18 years (diagnosed from 1 January 2017 to 30 June 2018) of Addis Ababa city. Taking the expected proportion (p=35.0%) of patient delay (>3 months) from a similar study,[19] assuming a 95% level of confidence, a 5% precision and 5% non-response rate, a minimum of 368 patients with breast cancer were required for the study. To increase the precision of the estimates, all available newly diagnosed female patients with breast cancer aged 18 years and above enrolled in the cohort (n=441) were considered in the analysis.

Setting and participants

The Ethiopian health service is structured into a three-tier health system: primary healthcare level, secondary healthcare level and tertiary healthcare level connected to each other by a referral system. The primary healthcare service points for urban settings like Addis Ababa include health centres, private clinics and primary hospitals, while secondary and tertiary healthcare levels are composed of general hospitals and specialised hospitals, respectively. Compared with hospitals, health centres are more likely to be staffed by nurses and health officers (graduate of a 4-year training programme in biomedical, clinical and public health courses), and they mainly provide preventive and primary care.[20] Specific to breast cancer, health centre staff are expected to create community awareness on the availability and importance of clinical breast examination services, and refer women suspected of breast cancer to general hospitals for diagnostic services.[21]

The study participants were recruited sequentially from seven public and private health facilities (Tikur Anbessa Specialised Hospital, St. Paul Hospital Millennium Medical College, Betezata Hospital, Hallelujah General Hospital, Landmark Hospital, Legehar Hospital and United Vision Medical Services Centre) in Addis Ababa city. These health facilities capture more than 90% of all women with breast cancer reported to the cancer registry in Addis Ababa. Recruitment of the study participants began on 20 March 2017 and ended on 31 July 2018.

On daily basis, the research assistant assigned in each of the selected seven health facilities identified eligible women while they were waiting to be seen by their physician by examining the medical chart for their place of residence and their pathology reports for the date of diagnosis. To avoid duplication, the medical chart of the recruited woman was coded on its top cover and plastered with yellow. Concurrently, the monthly report of the Addis Ababa cancer registry cancer notification form was assessed to identify eligible women who were not captured in the seven health facilities. These women were contacted by phone for their place of follow-up and convenient date and time to meet for our interview. Of the 444 patients approached, 441 (99.3%) provided informed consent to participate in the study.

Prior to the interview, study participants were informed about the purpose of the study and their right to refuse to participate or withdraw at any point during the study period. Then verbal consent was obtained from the study participants using Amharic, the national working language. The decision to use verbal consent was informed by a rapid ethical assessment we conducted to design the consent process of this project.[22] Based on this assessment, we found that most of the participants were not comfortable providing written consent.

Variables and measurements

We used the Aarhus statement criteria[23] for classifying patient and diagnostic intervals. Accordingly, patient interval was defined as the interval from the date of first recognition of symptoms (the time point when first bodily changes and/or symptoms are noticed) to the date of first clinical presentation (the date at which the patient first presented to a healthcare provider after first recognition of symptoms).[23] Those patients in whom breast abnormalities were first identified by physicians or mammography were excluded from our computation of patient interval (n=24).

Diagnostic interval was defined as the interval from the date of first clinical presentation to the date of pathological diagnosis (the date at which the first histological or cytological confirmation of this malignancy was

documented in the pathology report).[23] The date of diagnosis was taken from the patient's pathology report.

Information on time intervals and other information related to diagnosis of breast cancer was collected using a questionnaire adapted with modification from a similar study conducted in Rwanda.[24] Before being executed, the questionnaire was pretested for its cultural appropriateness and clarity. Trained nurses interviewed the eligible women individually in a semiprivate room in Amharic, when they presented for treatment. To minimise recall bias, only newly diagnosed patients were included in the study. The median length of time (IQR) between pathological diagnosis and interview was 30 (10–73.5) days. If the participants were unable to recall the exact date of first symptom recognition, they were asked to provide a month or year ('was it at the beginning, middle, or end of the year?'). For those who remembered only the month (n=232), the date was estimated as the 15th day of that month. If the participants only said the beginning, middle or end of the year (n=61), the estimated date was 15th of February, June or October of the year, respectively; for those who were only able to provide the year (n=44), the estimated date was June 30th of that year. Similarly, for those who could remember only the month (n=206) of first clinical presentation, the date was estimated as the 15th day of that month. If they only remembered the beginning, middle or end of the year (n=34), the estimated date was 15th of February, June or October of the year, respectively. For those who were only able to recall the year (n=25), the estimated date was June 30th of that year.[24] We performed sensitivity analyses excluding patients who had only remembered the beginning, middle or end of the year or a year for the date of first symptom recognition or clinical presentation (online supplementary table 1).

Data analysis

Data were analysed using Stata V.14. We computed descriptive statistics for each of the study variables. Categorical variables are presented as numbers and percentages. For numerical variables, we present means with their SD for those with normal distribution, and median and IQR for those variables with skewed distributions.

Similar to previous studies, patient[24–27] and diagnostic[19 28 29] delays were defined as >90-day patient interval and >30-day diagnostic interval, respectively. In cross-sectional studies, logistic regression is frequently used to estimate an OR as an association measure equivalent to the relative risk (RR). However, when the proportion experiencing an outcome exceeds 10%, an OR overestimates the RR and makes its interpretation unintuitive, and the prevalence ratio (PR) is a more accurate measure of association.[30 31] Thus, Poisson regression with robust variance was used to compute the adjusted PRs of the factors associated with the presence of patient and diagnostic delays. Variables reported in the literature as having an impact on patient and diagnostic delays, and those variables found to be associated (p value<0.25) with >90-day patient interval or >30-day diagnostic interval on univariable analysis were selected for the multivariable analysis model. The cut-off for p value at 0.25 for variable selection to multivariable analysis is supported by various literature.[32 33] Due to the lower sample size the variables had, woman's partner education (n=241) and woman's number of alive children (n=336) were not included in the multivariable regression model. Statistical significance was declared as having a two-sided p value of <0.05.

Patient and public involvement

Neither patients nor the public were involved in the planning or design of the study. However, we conducted a rapid ethical assessment among women with breast and cervical cancer, family members and healthcare providers for designing consent of study participants.[22]

RESULTS

Table 1 shows the sociodemographic characteristics of the 441 study participants. The mean (SD) age of the participants was 44.4 (12.2) years. Forty-five percent of the participants did not attend school or had only primary-level education. Seventy-four percent of the participants reported family income of less than US$194 per month; and 71% of the participants paid their medical expenses out of pocket.

One-third of participants (32.2%, 95% CI [27.9%, 36.6%]) had never heard of breast cancer, 73% of the study participants did not know how to do a breast self-examination and 9 in 10 patients had no history of clinical or mammographic breast examination before they noticed the first symptom of their illness.

A breast lump (78.0%) was the most common symptom recognised first, followed by pain (10.2%), change in colour of the nipple (4.8%) and breast discharge (4.3%). For 95% of the participants, the first symptom was self-detected. Among the self-detected participants, only 8.0% considered the first symptoms as possible symptoms of cancer, while 36% considered it as a simple breast swelling and 56.0% attributed to others (eg, sun stroke, cold exposure, menses, breast milk). Thirteen percent of the participants used traditional medicines such as holy water and visiting traditional healers before seeking medical consultation. Notably, 19% of the participants waited until they recognised progression of their breast cancer symptom(s).

The main triggers for seeking medical care were the first breast cancer symptoms (70.0%), followed by noticing progression of symptoms (14.1%) and persuasion from family members/friends (13.2%). Thirty-six percent of patients first had their symptoms assessed at a health centre, 40.5% at private hospital/clinic and 23.3% at public hospital. About a quarter of patients visited ≥4 different healthcare facilities (maximum 12 facilities), and 23% of the patients made ≥10 visits to healthcare facilities (maximum 21 visits) before final pathological diagnosis of their disease.

Table 1 Sociodemographic characteristics of women with breast cancer diagnosed from 2017 to 2018, Addis Ababa, Ethiopia (n=441)

Sociodemographic characteristics	Frequency	Percentage
Age at diagnosis (years)		
<30	40	9.1
30–39	145	32.9
40–49	106	24
50–59	82	18.6
60–69	54	12.2
> =70	14	3.2
Highest level of education		
Not attended school	87	19.7
Primary school (1st–8th)	112	25.4
Secondary school (9th–12th)	142	32.2
Diploma and above	100	22.7
Marital status		
Married	255	57.8
Widowed	73	16.6
Single	67	15.2
Divorced	46	10.4
Occupation		
Housewife (homemaker)	217	49.2
Employed outside the home	198	44.9
Retired	13	2.9
No job	13	2.9
Family size		
< =2	65	14.7
3–5	260	59
>6	116	26.3
Family monthly income (US$*)		
<61.0	125	28.3
61.0–194.0	200	45.4
194.0–403.0	81	18.4
>403.0	25	5.7
Unknown	7	1.6
No income	3	0.7
Source of medical expenses		
Out of pocket	313	71
Free medical care	103	23.4
Health insurance	25	5.6

*ETB=US$0.037.

Patient intervals

The median (IQR) patient interval was 30 (6–132) days. More than a third (35.7%, 95% CI [31.1%, 40.3%]) of the patients waited for longer than 3 months before seeking medical care, and 11% of the patients waited for over a year (online supplementary table 1). When patients who waited >3 months to seek medical care were asked their main reasons, 69% of them said "not bothered by the problem at first," followed by using holy water/visiting traditional healers first (17.4%), and unable to take time off from work (12.7%) (online supplementary table 2).

Diagnostic intervals

The median (IQR) diagnostic interval was 69 (22–213) days. More than two-thirds (69.1%, 95% CI [64.6%, 73.3%]) of the patients waited for longer than a month and 18% of the patients waited more than a year to receive diagnostic confirmation after their initial medical presentation (online supplementary table 1). The most common reasons given by the patients for extended diagnostic delays (over a year) include both provider factors such as misdiagnosis (25.6%), false-negative laboratory results (3.8%) and lack of empathy at first medical consultation (3.8%), and patient factors such as use of traditional medicine (20.5%), fear of cancer diagnosis and treatment (especially breast surgery) (17.7%), lack of awareness about disease severity (6.4%), and financial barriers for diagnosis and treatment (3.8%) (online supplementary table 2). By type of health facilities visited for first medical consultation, the median diagnostic interval ranged from 89 days among patients who visited health centres to 55 days among those patients who visited public hospitals. The median number of visits to healthcare facilities before diagnostic confirmation varied from eight visits among patients who visited health centres to four visits among those who visited public or private hospitals/clinics.

Factors associated with patient and diagnostic delays

In unadjusted analysis, women's age ≥60 years (PR = 1.47, p = 0.030), women who did not attend school (PR = 2.19, p = 0.000) or complete secondary school (PR = 1.63, p = 0.025), having partner who did not attend school (PR = 2.04, p = 0.006), having ≥5 children (PR = 1.61, p = 0.009), never having heard of breast cancer before symptom recognition (PR = 1.34, p = 0.024) and using traditional medicine before consultation (PR = 2.31, p = 0.000) were significantly associated with higher prevalence of patient delay. After adjustment, using traditional medicine before consultation (adjusted PR = 2.13, 95 CI% [1.68, 2.71]) was the only factor significantly associated with increased prevalence of patient delay (online supplementary table 3).

After adjustment for the participants' sociodemographic variables, having first consultation at a health centre (adjusted PR = 1.19, 95% CI [1.02, 1.39]) and visits to ≥4 health facilities before confirmation (adjusted PR = 1.24, 95% CI [1.10, 1.40]) were significantly associated with increased prevalence of diagnostic delay. In contrast, consultation after recognition of symptom progression (adjusted PR = 0.73, 95% CI [0.60, 0.90]) was associated with lower prevalence of diagnostic delay (online supplemental table 3).

DISCUSSION

We found that women with breast cancer in Addis Ababa have prolonged patient and diagnostic intervals, with one-third of the patients waiting for >3 months before seeking medical care, and nearly one-fifth of the patients waiting over a year before receiving diagnostic confirmation. In addition, about a quarter of patients visited ≥4 different healthcare facilities, and a quarter of the patients made ≥10 visits to healthcare facilities before diagnostic confirmation.

In our cohort, the proportion of patient delay was substantially lower than those found in two single institution-based studies in Addis Ababa.[16 17] These differences may reflect differences in the study participants' residence and improvement in patients' awareness over the last 13 years (2003–2015) since the previous studies were conducted. About one-third of the patients in the single-institution based studies[16 17] resided outside of Addis Ababa, and patients residing outside the city have been reported to have less knowledge about breast cancer and less access to healthcare services.[6]

Similarly, compared with studies in sub-Saharan African countries, the median patient interval in our study (30 days) was considerably shorter than those reported from Rwanda (150 days)[24] and Mali (144 days),[34] but comparable with that reported from South Africa (23 days).[35] As expected, compared with findings from countries outside of sub-Saharan Africa, however, our finding of median patient interval is generally longer.[36 37]

Knowledge on the risk of breast cancer, screening and other early detection methods, initial symptoms, and its treatment is important for appraisal of first symptoms and for seeking timely medical care.[38–40] However, a third of the women with breast cancer in our study had never previously heard of breast cancer. Only 8% of the patients suspected their first symptom to be a symptom of breast cancer. A substantial proportion of patients either disregarded the clinical importance of the first symptoms or attributed them to other non-specific conditions. Sharp *et al* identified 'knowledge deficit a modifiable factor' as a main barrier to early detection of breast cancer in Uganda.[12] In addition to the patients, our findings suggest the presence of providers' oversight of initial breast cancer symptoms leading to delayed referral of the patients for confirmation. These findings underscore the need for programme to enhance knowledge about breast cancer symptoms among the general public and healthcare providers.[41 42]

Birhan *et al* reported that cancer patients were among the most common visitors to traditional healers in Addis Ababa.[43] Thirteen percent of our study participants' immediate response to the first breast cancer symptoms was using traditional medicines, which was significantly associated with increased prevalence of patient delay. This practice has been shown to affect patients' decision to seek timely medical care[35 38] and to prolong patient interval in Ethiopia[16 17 44] and other parts of Africa.[24 34 45] This is partly due to the belief that cancer is fatal and incurable by conventional medical treatment.[44 46]

Our finding of median diagnostic interval (69 days) was lower than that reported in Rwanda (150 days)[24] but longer than those reported in Mali (27 days)[34] and South Africa (28 days).[35] Sixty-nine percent of the patients in our study waited for >30 days, and 18% for over a year to receive diagnostic confirmation following first medical consultation for their disease. Provider factors that may have contributed to this considerably prolonged diagnostic interval, as reported by the patients, include difficulties of navigating the healthcare system, misdiagnosis of clinical manifestations and false-negative laboratory results. Although our study has not explicitly estimated the pathology result turnaround times, some portion of the diagnosis delays we observed could be attributed to prolonged pathology result turnaround times in the few available diagnostic facilities in the city. Similar to other sub-Saharan countries,[47] patients with cancer in Addis Ababa waited on average for 15 days to get the pathology result.[9]

In the multivariable analysis, diagnostic delay was associated with first consultation at a health centre, and visits to ≥4 healthcare facilities before diagnosis confirmation. On average, patients visited at least three different healthcare facilities and made about seven visits before receiving diagnostic confirmation. The number of visits was substantially higher among those patients whose first consultation was at a health centre, in part because of the additional time needed for referring patients to hospitals.[20] This may also reflect a low level of breast cancer knowledge among both providers and patients in the health centres, as health centre providers are more likely to be nurses or health officers than doctors, and patients visiting health centres are more likely to be less educated compared with those visiting private clinics or hospitals. A study conducted among female nurses[48] in Addis Ababa found poor general knowledge about breast cancer.

In contrast, patients who sought medical consultation after progression of symptom(s) had lower prevalence of diagnostic delay. This is likely because more extensive breast symptoms or signs may have led to prompt referral of patients to diagnostic centres as reported elsewhere.[49 50]

Similar to other literature,[51–53] patient-related factors such as belief in traditional medicine, fear of cancer diagnosis and treatment, refusal of breast removal, and time and financial barriers were also reported as influencing the diagnostic interval.

There are no breast cancer screening services in Addis Ababa or other parts of Ethiopia. Therefore, early diagnosis is dependent on patients' decision to seek care after initial recognition of symptoms, and healthcare providers' timely evaluation and referral for confirmation. This study was conducted in the capital city, Addis Ababa, where the population has better access to health information and service compared with the rest of Ethiopia.[6] A substantial number of women with breast cancer in the city experienced prolonged patient and diagnostic intervals due to both individual and health system-related factors. Provider delay is more common than patient delay. This may in part reflect lack of referrals to a specialised centre for a substantial

proportion of patients with suggestive signs and symptoms of breast cancer, which in turn calls for training of front-line health workers to improve their clinical suspicion skills and early referral. Moreover, strengthening the referral linkage between the health centres and the hospitals could increase early detection of breast cancer.

To our knowledge, this study is the first multicentre study on extent of patient and diagnostic delays of breast cancer and associated factors in Ethiopia with incident cases recruited from seven major health facilities in Addis Ababa, representing about 90% of all incident breast cancer cases in the city. However, our study has limitations. First, information about the dates of symptom recognition and medical consultations was dependent on the participants' memory and therefore may not be free of recall bias. However, we have attempted to mitigate recall bias by restricting our study participants to those newly diagnosed cases and using local events to recall the date of first symptom recognition and presentation. We additionally performed a sensitivity analysis and found no statistically significant difference in the association results (adjusted PRs) and the proportions of women across the different cut-points of time intervals, except for those who waited for less than a month and more than a year before consultation. This may be because patients who waited on consultation for more than a year are less likely to remember the date of first symptom recognition than those who consulted within a year of their symptom recognition. Inclusion of these patients in the analysis pooled the estimates across the different cut-points of time intervals (≤30 days, 31–90 days, 91–180 days, 180–365 days and >365 days) towards the highest waiting interval (>365 days), while exclusion of these patients from the analysis pooled the estimates towards the lowest waiting interval (≤30 days). Thus, we would not expect our estimation strategy to bias our results in a particular direction. Second, the date of diagnosis was taken from the pathology report; however, this may not reflect when the patient received the diagnosis. Third, the interviews were conducted in a hospital setting, which could have resulted in a social desirability bias leading to under-reporting of patient and diagnostic delays and over-reporting of desirable behaviour such as self-breast examination. Fourth, it is possible that the long waiting period for some of the cases may reflect indolent breast cancer cases[54] or benign breast conditions. Fifth, the study was a hospital-based study, and thus might not capture the experience of women who solely seek care elsewhere (eg, traditional or spiritual healers) or women who are seen only at primary care facilities and do not get to the hospital. Lastly, our study may be underpowered to detect a significant association for some of the independent variables.

CONCLUSIONS

In this multicentre study, we have found that substantial proportions of women with breast cancer in Addis Ababa have prolonged patient and diagnostic intervals attributed to modifiable patient and healthcare provider factors such as poor knowledge about breast cancer, downplaying the importance of the first breast cancer symptoms, preference of traditional and spiritual remedies, provider's oversight of the first symptoms and delayed referral of women for confirmation with suggestive of breast cancer symptoms. These underscore the need for public health programme to increase knowledge about breast cancer among the general population and healthcare providers in the city in order to reduce the morbidity and mortality associated with the disease.

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RESEARCH ARTICLE

Perspectives of patients, family members, and health care providers on late diagnosis of breast cancer in Ethiopia: A qualitative study

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Abstract

Background

Most women with breast cancer in Ethiopia are diagnosed at an advanced stage of the disease, but the reasons for this have not been systematically investigated. This study, therefore, aimed to explore the main reasons for diagnosis of advanced stage breast cancer from the perspective of patients, family members, and health care providers.

Methods

A qualitative study with in-depth interviews was conducted with 23 selected participants at Tikur Anbessa Specialized Hospital, Oncology Clinic using a semi-structured interview guide. These participants were 13 breast cancer patients, 5 family members, and 5 health care providers. Data were transcribed into English, coded and analyzed using thematic analysis.

Results

Awareness about the causes, risk, initial symptoms, early detection methods, and treatment of breast cancer were uncommon, and misconceptions about the disease prevailed among breast cancer patients and family members. There was a sense of hopelessness and uncertainty about the effectiveness of conventional medicine amongst patients and family members. Consequently, performing spiritual acts (using holy water) or seeking care from traditional healers recurred amongst the interviewees. Not taking initial symptoms of breast cancer seriously by the patients, reliance on traditional medicines, competing priorities, financial hardship, older age, fear of diagnosis of cancer, and weak health systems (e.g., delay in referral and long waiting period for consultation) were noted as the main contributors to late diagnosis. In contrast, persuasion by family members and friends, higher

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educational attainment, and prior experience of neighboring women with breast cancer were mentioned to be facilitators of early diagnosis of breast cancer.

Conclusions

The causes of late diagnosis of breast cancer in Ethiopia are multi-factorial and include individual, cultural, and health system factors. Interventions targeting these factors could alleviate the misconceptions and knowledge gap about breast cancer in the community, and shorten waiting time between symptom recognition and diagnosis of breast cancer.

Introduction

Cancer is becoming a major public health problem in most economically developing countries, including Ethiopia [1]. In Ethiopia, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women [2], accounting for about 32% of the total cases [3] and 19.4% of all cancer deaths [4]. Further, over two-thirds of breast cancers in Ethiopia are diagnosed at late stages of the disease [5]. In addition to the late stage at diagnosis, access to evidence-based treatment is limited in Ethiopia, resulting in poor survival [5, 6].

A previous systematic review conducted by Espina and his colleagues has summarized the reasons for delayed diagnosis of breast cancer patients in Africa. The main reasons noted by this study were low educational attainment, lack of awareness on breast cancer and its detection methods, type of initial symptoms, fear of the disease or its treatment, traditional medicine use, financial difficulties, lack of access to healthcare, number and type of health care providers contacted before diagnosis, delayed referrals or non-referrals, misdiagnosis, wrong advice or false reassurances, and delays in obtaining diagnostic confirmation [7]. This review was mainly based on quantitative studies, and it may not have captured information that could be elucidated from qualitative studies through probing of participants [8]. In addition, the studies included were all based on data obtained before 2014. Since then, various changes have occurred within Ethiopia and Africa such as more political attention to cancer care [9], but late stage disease presentation is still a major problem [10]. The Ethiopian National Cancer Control Plan was drafted in 2015 for the period of 2016–2020 aimed at improving early diagnosis of cervical and breast cancer. For cervical cancer, the government has purchased hundreds of cryotherapies to implement visual inspection with acetic acid in major hospitals in the country. For breast cancer, the government plans to promote early detection of symptomatic breast cancer patients and screening asymptomatic high risk women through promoting breast self-awareness, and clinical breast examination for all women coming to health institutions for other conditions [11]. In addition, the government is constructing five regional cancer treatment centers, subsidizing the procurement of lifesaving chemotherapy for all public facilities, training more health professionals (oncology specialists, nurses and pharmacists), and collaborating with different partners to build the capacity of the health care providers.

Understanding the recent specific barriers to early diagnosis that Ethiopian breast cancer patients are facing is important for planning targeted interventions that help to mitigate premature death of women from breast cancer [12]. Initial exploration using qualitative research methods were considered most appropriate because these methods allow for an in-depth understanding of opinions, thoughts and feelings of respondents, and obtaining more contextualized information on the barriers encountered by the respondents [13]. However, there are few qualitative studies which used first-hand patient narratives to explore the specific barriers

to early detection of breast cancer among breast cancer patients in Ethiopia. Dye and his colleagues, using mixed methods, have investigated the experiences of initial symptoms and actions [14], patient navigation [15] and beliefs and practices [16] of breast cancer in Ethiopia. These studies have documented that a substantial proportion of women with breast cancer first seek care in the form of traditional medicine, waited for about one and half year before medical consultation, and face difficulties in navigating the healthcare system for timely diagnosis of their cancer. However, these results were based on data collected approximately 10 years ago and were limited to the beliefs and practices of patients. Hence, the evidence from these studies may not reflect the current causes of late diagnosis of breast cancer in the country in view of the rising burden of the disease and changing healthcare system.

In this study, we investigated both patient and health system-related reasons for late diagnosis of breast cancer from the patients', family members', and health care providers' perspectives in Addis Ababa. The information obtained from this study will help identify gaps and barriers to early diagnosis. It also provides fact-based material to develop "stories" that illustrate the compelling need of improved care.

Methods

The study was conducted at Tikur Anbessa Specialized Hospital (TASH) Oncology Center. TASH is a teaching hospital of the College of Health Sciences of Addis Ababa University, and tertiary referral hospital for the country. The hospital has a separate building for cancer treatment (oncology clinic). This hospital was chosen because it is the referral hospital for cancer care and hosts the only radiotherapy machine in the country.

Study design

A phenomenological study was used to explore the barriers for early diagnosis of breast cancer. Phenomenological method is useful in studying participants' lived experiences of a phenomenon, which in this case is the experience of breast cancer diagnosis, from patients, family members and health care providers' perspective [17]. This study was conducted as a baseline to a broader ongoing follow-up study in Addis Ababa documenting the experiences of women with breast cancer from recognition of symptoms to diagnosis, treatment, and survivorship, and end of life [18].

Recruitment of study participants

A total of 23 In-depth Interviews (IDI) were conducted with 13 breast cancer patients, 5 family members, and 5 health care providers. Participants were recruited through purposeful sampling [19]. Women aged 18 years and above who were diagnosed with breast cancer in 2016 and treated at the oncology clinic from March–July 2017, were included in the study. Similarly, family members aged 18 years and above who accompanied breast cancer patients were included in the study. Health care providers who had a minimum of bachelor degree in health science, and have been providing care to cancer patients at the oncology clinic for more than a year were included in the study. The sample size was determined based on information saturation; recurrent patterns became evident in the participants' narrations [20].

Interviews

Eligible participants were identified with the help of the head nurse of the oncology clinic. After we obtained willingness to participate, an appropriate place and time for an interview was arranged. Interviews were conducted face to face with participants individually in a private

room which was either in the cancer registry office or head nurse's office of the oncology clinic. The primary investigator (AG) and three public health experts who had a Master in Public Health and experienced in qualitative research conducted the in-depth interviews. The four interviewers (2 males and 2 females) were paired into two groups consisting one note taker and one interviewer. None of the interviewers worked at the oncology clinic, therefore, the interviewers likely had no direct influence on the interview responses.

A semi-structured interview guides were used to interview the three groups of respondents: breast cancer patients, family members and health care providers. Different interview guides were used for the three target groups (S1 File). The interview guides consisted of open-ended questions. For instance, some of the questions asked to the breast cancer patients were: "What is known about breast cancer in the community? Have you ever heard of breast cancer before you recognized the first symptoms of your illness? Tell me about your experience with breast cancer from the first symptoms recognition to diagnosis? What are the major challenges you have faced during diagnosis? Why do breast cancer patients seek medical care late? (What affected that), and What measures do you suggest to make sure breast cancer diagnosis happens early?" In addition to these main questions, the interview guide included probing questions.

Interviewers guided the respondents during the interview until all of the questions listed in the interview guide were inquired. Probing was used to inquire further explanation of the responses of the participants. All of the interviews were audio-recorded. Field notes were recorded during the in-depth interview to include keynotes, observable non-verbal cues of the participants. Each of the interviews took 40 minutes on average.

Data analysis

The transferability of the findings was ensured by using person triangulation [19]: data were collected from three groups of participants (patients, family members and health care providers) to triangulate and validate the findings. This helped to generate a more comprehensive data. The data collectors and investigators were debriefed on a daily basis to discuss themes and issues for exploration, and to verify saturation of information. Audio data were transcribed verbatim into Microsoft Word files. All transcripts of the interviews were checked for errors by simultaneous reading of the transcripts with the audio-recorded voices. Each transcript and corresponding field notes were read thoroughly to gain a sense of the respondent's experience as a whole. Verbatim transcripts of the data were imported into NVivo software version 11 for computer-based data coding and reduction without compromising the central idea. Line-by-line coding was then conducted by the primary investigator (AG). Codes were compared based on their differences and similarities, and sorted into categories. Categories then were grouped into themes, which were analyzed using thematic analysis [21]. Quotes that best described the various categories and expressed what was said frequently in several groups were chosen, and presented in italics.

Ethical considerations

The study was approved by Institution of Review Board of Addis Ababa University College of Health Science (ref: 018/17/SPH) and participants provided fully informed consent to participate by reading a participant information sheet and signing a consent form.

All documents were kept private and confidential. All audio-recorded interviews were reviewed by the transcriber and the principal investigator only, and each participant was identified by specific code number, rather than by name.

Results

A total of 23 in-depth interviews were conducted with breast cancer patients, family members, and health care providers of Tikur Anbessa Specialized Hospital Oncology clinic (Table 1).

Based on thematic analysis, the responses of the participants revealed eight common reasons for late diagnosis, and three factors contributing to early diagnosis.

Reasons for late diagnosis of breast cancer

Lack of awareness about breast cancer in the community. The study participants revealed a low level of awareness of breast cancer. Before they recognized the first breast cancer symptoms, breast cancer-related discussions and screening were uncommon. Almost all of the breast cancer patients had never heard of breast cancer before they sought treatment for their illness.

"Before I recognized the first symptom of my illness, I have never heard of breast cancer. Rather, I heard women say I have pain in my breast. . ." (P08)

". . . People in my community are not aware of breast cancer or they have wrong information about cancer. . ." (HP04)

Disregarding or misattribution of breast cancer symptoms. The majority of the patients noticed a painless breast lump or swelling accidentally. The painless nature of the lump made the patients disregard its potential severity, and they usually attributed it to non-cancer illness, mainly sun stroke, locally known as "mitch". One breast cancer patient who initially noticed a painless lump waited for about a year without seeking any medical care. Once she noticed her nipple inverted, she worried and sought medical care.

"I thought it was just a disease not as severe as this. . . I thought it was caused by the smell from the place I worked at. . . I thought it was something related with mitch . . ." (P02)

Table 1. Study participants' characteristics and code, TASH, Oncology Clinic, Addis Ababa, Ethiopia, 2017.

Socio-demographic Characteristics	Breast cancer patients (P01-13)	Family Members (R01-05)	Health Care Providers (HP01-05)
Participants age* (years)			
<40	7	3	-
40–50	5	1	-
>50	1	1	-
Highest level of education			
Not attended school	7		
Primary school (1-8th)	5	1	
Secondary school (9-12th)	2	1	
Diploma and above	1	2	
BSc. Degree		1	3
MSc. Degree			2
Occupation			
Housewife (homemaker)	2		
Employed outside the home	8	3	
No job	3	2	
Health care providers			5

P: breast cancer patient; R: Relatives; HP: Health Care Providers BSc.: Bachelor of Science, Master of Science

*the age of health care providers is omitted to keep anonymity

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"I noticed a small swelling in my breast. But I was not worried about it. It started to extend its tail to my arm pit. Then I went to the health center. They told me to go to the hospital. . . I did not trust them. I considered the disease as nothing. When I felt severe pain, I returned back to the healthcare facility. The doctor became visibly angry at me." (P01)

Misperceptions about breast cancer treatment and its outcomes. The study participants noted the presence of delusions about the causes, treatment and outcomes of cancer among the patients and their community. Amongst interviewees (patients and family members), many had no response to the question *"what do you think is the cause of breast cancer?"* However, they speculated on the causes of breast cancer based on their own perspectives and their communities. The speculated causes include sun stroke (M*itch*), supernatural force as a punishment for their sins, evil eye, use of contraceptive, blunt trauma to their breast, failure to breastfeed, poor breast care, inheritance, and climate change. "*Mitch*" was a recurrent speculated cause of their illness, as some believe it to be related to prolonged exposure to sunlight, especially during baking and preparing food at open field (out of the home or shelter), and prolonged exposure to food odor during cooking.

". . . Mine is caused by mitch because of excessive sun exposure. It happened when I took off my shirt during the hottest time of the day while working as a street vendor." (P02)

". . . They (women with breast cancer) feel like they did sinful things to deserve such disease. Some of the patients relate the disease with the things they eat and drink or smoke. . ." (HP03)

A common view amongst interviewees was that cancer is a severe, deadly and incurable disease. There was a sense of hopelessness and fear of death from cancer amongst interviewees (patients and family members). These views were expressed mainly due to the doubt they had on the effectiveness of the conventional treatment. Such views were prevailing in those who were considered aware of cancer and those who had a bad experience.

"How am I going to forget about the disease? I am carrying it. . . I think that I am going to die. . . other women also think that the disease cannot be cured and the person who has it is just waiting to die." (P09)

". . .I told you that people think cancer as a fatal disease . . .That was how my mom felt. She tried to give us everything and did not even think about herself at all. She perceives as she does not have life after the incidence." (R03)

". . . Some patients totally give up and refused to take the treatment. They preferred to go to traditional places/ holy water. . ." (HP05)

Non-medical management of breast cancer symptoms. Performing spiritual acts (such as using holy water) or seeking care from traditional healers was common amongst the breast cancer patients and family members interviewed; this was commonly the primary response to the first symptoms. Medical consultation was often only then considered if the patients did not consider these remedies successful. It was not unusual for subjects ignore the medical advice received, and return home to use different traditional medicines.

". . . I went to a traditional healer and he provided me an ointment, which I used for about 4 months. Then there was no change with the swelling. . . I waited for more than a year without visiting health facility . . ." (P12)

". . . There were people who completely healed by holy water. . . While I was in the hospital, one of my relatives advised me not to get breast surgery and rather to go to a traditional healer (Name). But I refused her advice . . ." (P06)

". . . There is traditional medicine even in Addis Ababa (capital city). . . . They insert something to the affected breast using syringe. They say that the medicine will get rid of the cancer from the breast . . ." (P02)

Fear of cancer diagnosis. Though issues related to fear of diagnosis were not particularly prominent in the interviewees, few reported fearing the confirmation of their diagnosis. This fear was mainly attributed to what the participants had heard in the community about the severity of cancer. A common view among interviewees was that in their community the word cancer is dreaded as incurable and fatal, and that cancer is difficult to talk about because of this perception.

"I do not know. When I recognized my first symptoms, I thought I will die of the disease immediately if it turns out to be cancer. I was afraid of going to the health facility . . . I lost my hope because in the community, cancer is known as an incurable disease. It is called a killer." (P02)

Almost all of the in-depth interviewees (patients and family members) revealed that confirmation of breast cancer was a shocking and scaring news for the clients and their families. This was due to low suspicion of breast symptoms as a sign of cancer, perceived seriousness of cancer, uncertainty about effectiveness of conventional treatments, and changes in body image after surgical removal of breast cancer. The interviewees explained their feelings on mastectomy as follow:

"Oh, my God, I felt many things, having a breast removal at old age . . . I had no pain at all. I felt why I have to go through breast removal at this age. I should die and get buried with dignity. I felt very sad." (P13)

". . . They say that it is shameful if someone hears about it . . . A person should die with full body parts, but part of the body will be lost due to the breast removal." (R03)

". . . He (physician) told me that he has to cut out my whole breast; and I was shocked and cried." (P06)

Competing priorities. Multiple interviewees responded that family responsibilities, such as looking after children, and the inability to take time off from work were their reasons to pay little attention to their first symptoms, usually a painless lump, of the breast illness.

". . . We have children who should go to the school; we need to prepare food. . . We have a lot of work. . . You cannot leave them and run to the health facility." (P05)

Financial insecurity. The cost of transportation, investigation and treatment was also mentioned as a reason for late diagnosis. There were patients who reported returning home after being referred to a higher health facility for financial reasons, while others reported selling their property or borrowing money to get medical care.

". . . I went to the health center. They told me to go to the hospital, but I did not have money to go to the hospital. Instead, I went to my home and stayed for months." (P01)

". . . We had no money. We were forced to sell our cattle and our crops to cover the medical cost. . ." (P05)

". . . I thought the cost of diagnosis was cheap, but it cost me 7500 birrs . . . I borrowed money from different sources as I did not want to see my wife die." (R01)

Health system-related barriers. Physicians misunderstanding of the first symptoms (telling patients not to worry about their symptoms), inappropriate reassurance as the lump is benign without biopsy, long waiting times to receive diagnostic confirmation, few diagnostic centers, patient load, and poor provider-patient communication and counseling were all reported as reasons for late diagnosis of breast cancer.

". . . I noticed something a small lump on my breast . . . I woke up in the morning and went to my doctor. He told me it could be a tumor. I asked him if it could be a cancer because I heard about it on TV. He told me it is not a cancer." (P07)

". . . There is long waiting time to get treatment. As a result, many people are at higher risk of death . . ." (HP01)

Facilitators of early diagnosis of breast cancer

Persuasion by family members and friends. We found that family members and friends had a positive impact on the decision of patients to seek medical care.

". . . The influence of my friend working in the hospital made me seek medical care . . . Had she did not push me, I would not have sought medical care. . . ." (P06)

Prior knowledge of someone with breast cancer. Knowing someone who was treated for breast cancer was reported to be a facilitator of early medical consultations.

". . . I know a mother who was treated for breast cancer. When I felt lump in my breast, I was shocked and immediately went to the hospital . . ." (P04)

The literacy level of the women. Interviewees felt that women at a younger age with higher literacy level were more likely to be early health care seekers compared to older or less literate women. These views expressed mainly in relation to the role of education on women's interpretation of the first symptoms of breast cancer and decision to seek medical care.

"Younger women are better in seeking care. Older women did know nothing. . ." (P08)

"Those who are educated are more likely to seek care earlier. . . It is due to lack of knowledge. . ." (P05)

Participants' suggestions to mitigate late diagnosis

In all cases, the informants suggested public health campaigns and programs to enhance awareness about breast cancer symptoms, signs, and benefit of early identification and treatment as an approach to mitigate the rising burden of the disease in the country. Involving breast cancer survivors in breast health education as community educators was also suggested.

". . . We should use breast cancer survivors to educate the community that cancer can be cured if patients seek medical care as soon as they noticed the symptoms. . . I can teach the

community about what I experienced with the breast cancer. I do not think any one of the breast cancer survivors will disagree to educate the community and save the lives of other women." (P03)

The participants emphasized the importance of regular breast self-examination and seeking medical attention immediately following recognition of abnormal breast symptoms. The participants also suggested that interventions by the healthcare system to establish and expand counseling services, to reduce waiting times for diagnosis and treatment (expand diagnostic and treatment centers), and to mitigate the financial burden of cancer in patients and family members.

". . . The burden of the disease is increasing; most of the services, however, are given in Tikur Anbessa Specialized Hospital only. Therefore, the government should open more facilities providing such services and strengthen follow-up of patients." (P06)

Discussion

This study explored both patient-related and healthcare system-related reasons for late diagnosis of breast cancer from patients', family members', and health care providers' perspectives. Information on breast cancer risk factors, methods of early detection, initial symptoms, and its treatments are important for encouraging women to seek medical care immediately after recognition of the first symptoms [22, 23]. Our study, however, revealed a poor community awareness and common misperceptions about breast cancer, with little recognition of susceptibility or the benefits of early care seeking after symptom recognition. Because of poor knowledge about breast cancer, women are less likely to perceive the disease as severe and seek medical care if they are not acutely sick [24]. As a painless lump is the common initial presentation of breast cancer, many women disregarded the clinical importance of the first symptoms. Family responsibilities and inability to take time off from work increased the risk of disregarding the severity of the first symptoms. In accordance with these results, previous studies [25, 26] have demonstrated that women's family engagements and job commitment are an important contributor to late/delayed medical consultation.

Moreover, it was rare to suspect cancer as a cause of the first symptoms of their breast illness. Most of the time the first symptoms of breast cancer were misinterpreted as resulting from non-cancer illnesses such as sun stroke, locally termed "mitch". In Ethiopia, "mitch" is a local and common terminology used to explain a wide range of nonspecific illnesses in the community [27, 28]. Such beliefs triggered women to delay medical consultation while practicing different home remedies, spiritual acts and traditional medicines intended to treat the perceived cause of their illness, "mitch". The misattribution of the symptoms is related to the women's low perceived susceptibility to breast cancer, and poor awareness of the initial symptoms of breast cancer [29]. Similar to our findings, a previous quantitative study conducted in Addis Ababa found that more than half of women had poor knowledge about breast cancer [30]. Thus, increasing awareness of the signs and symptoms of breast cancer in the community could help to minimize such negligence and misattribution of the first symptoms of breast cancer.

Contrary to the misinterpretations of the symptoms, an initial suspicion of cancer deters women from seeking medical care immediately after they recognize the symptoms. This is mainly due to the view in the community that cancer is a deadly disease, and incurable with the existing conventional treatment in the country. Similar perceptions were noted in other

studies from Ethiopia [16, 31], India [23], and Iran [26], and studies have reported women refraining from visiting health facility for fear of a confirmed cancer diagnosis [26, 31, 32]. This finding suggests that educating the community about the benefits of early diagnosis and treatment initiation could help to correct the misperceptions and improve health-seeking behavior of women with symptoms suggestive of cancer [33].

Previous studies in Ethiopia have documented that a significant number of people prefer visiting traditional healers before seeking medical care [24, 34]. Similarly, our study revealed that use of traditional medicine was common and the main cause of late diagnosis. For some of the breast cancer patients, seeking medical care was their second option, and only after traditional medicine failed to provide hope of a cure. Such practices have also been noted in other studies [34–36]. Together with late recognition of the first symptoms, the time elapsed on using traditional medicine could further advance stage of the disease and complicate its treatment outcomes. Therefore, involvement and working with traditional healers to create awareness about the symptoms of breast cancer and benefit of early diagnosis could benefit the women who visited the traditional healers for the complaint of breast abnormality.

The affordability of medical care [24] and quality of the health service [23, 37] determine the health care utilization of women who decide to seek care. Shortcomings in either of these could affect a woman's decision to seek care from the health facilities or push them to seek care from traditional healers [31]. In our study, health system-related factors such as access to healthcare, physicians misunderstanding of the first symptoms, inappropriate reassurance of lump as a benign disease without biopsy, and poor counseling of patients presenting with signs and symptoms suggestive of breast cancer were noted as contributor to late diagnosis. Previous literatures have also revealed that health care providers' failure to appraise the first symptoms of breast cancer appropriately, and misdiagnosis contributed to delayed diagnosis and disease advancement [26, 32, 38]. This may call the need for training primary health care providers [39, 40] to recognize the first symptoms of breast cancer, and increase the suspicion of breast cancer at first contact. Moreover, breast cancer patients need appropriate advice and discussion on their problem, its consequences and treatment decisions [41]. Most of the breast cancer patients were not ready to accept the diagnosis of their disease as cancer. Often, women became emotionally disturbed at the time of confirmation because of their low suspicion of being diagnosed with breast cancer, perceived fatality of cancer, uncertainty with the effectiveness of the conventional treatment, and fear of losing their breast through surgical treatment.

In contrast to the above barriers, the persuasion by family members and friends was found to be a facilitator for patients to seek medical consultations after they recognized breast cancer symptoms and to make the decision to undergo surgical treatment. This finding has also been documented in a previous study conducted among breast cancer patients and proxies in the same study area (Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia) [14].

Early detection is the primary strategy for preventing premature death from breast cancer. Hence, interventions targeted at alleviating the above modifiable barriers [23] must be established in Ethiopia to diagnosis breast cancer at earlier stages. In settings, like Ethiopia, with no breast cancer screening service, early detection is mainly dependent on woman's knowledge on breast cancer [12], performing regular breast self-examination and immediate medical consultations after recognition of breast abnormalities [42, 43], and immediate health care providers' referral for confirmation [44]. Our study participants also emphasized the importance of breast self-examination, early medical care seeking, awareness creation and cancer pathology center expansion to improve early detection. Moreover, the study participants emphasized the importance of using breast cancer survivors as community educators to enhance community awareness of breast cancer. Though the effectiveness of this approach has not been investigated in our country, engaging breast cancer survivors as breast health educators [45–47] has led to

significant improvement in the knowledge and prevention of breast cancer morbidity and mortality.

Our study included different groups of participants, which helped us to triangulate our findings and examine the reasons of late diagnosis from different perspectives. We attempted to interview recently diagnosed patients, however, recall of past events with a foresight of experience may unconsciously make the stories of these women biased and inaccurate in explaining their experience.

Conclusions

The reasons for the late diagnosis of breast cancer among women in Ethiopia are multi-factorial and include individual, cultural, and health system factors. Interventions targeting these factors could alleviate the misconceptions and knowledge gap about breast cancer in the community, and shorten waiting time between symptom recognition and diagnosis of breast cancer.

Supporting information

S1 File. In-depth interview guide. Interview guides for breast cancer patients, family members, and health care providers at Tikur Anbessa Specialized Hospital oncology clinic.
(PDF)

S2 File. De-identified excerpts. Themes and sub-themes based on analysis of open-ended responses.
(PDF)

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CLINICAL TRIAL

Factors associated with late-stage diagnosis of breast cancer among women in Addis Ababa, Ethiopia

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Abstract

Purpose Stage at diagnosis is a key determinant of breast cancer prognosis. In this study, we characterize stage at diagnosis and determine factors associated with advanced stage at diagnosis among women diagnosed with invasive breast cancer in Addis Ababa, capital city of Ethiopia.

Methods Stage information was collected from medical records of 441 women with invasive breast cancer seen in seven major health facilities in Addis Ababa, from January 2017 to June 2018; these seven facilities capture 90% of all incident breast cancer cases in the city. We used multivariable Poisson regression model with robust variance to determine factors associated with advanced stage at diagnosis.

Results The predominant tumor histology was ductal carcinoma (83.7%). More than half of the tumors' grade was moderately or poorly differentiated. The median tumor size at presentation was 4 cm. Sixty-four percent of the patients were diagnosed at advanced stage of the disease (44% stage III and 20% stage IV), with 36% of the patients diagnosed at early-stage (5% stage I and 31% stage II). The prevalence of advanced stage disease was significantly higher among women who used traditional medicine before diagnostic confirmation (adjusted prevalence ratio [aPR] = 1.31; $p = 0.001$), had patient delay of > 3 months (aPR = 1.16; $p = 0.042$) and diagnosis delay of > 2 months (aPR = 1.24; $p = 0.004$). But it was lower among women who had history of breast self-examination (aPR = 0.77; $p = 0.021$).

Conclusions Advanced stage at diagnosis of breast cancer among women in Addis Ababa is strongly associated with use of traditional medicine and with prolonged time interval between symptom recognition and disease confirmation. Community- and health systems-level interventions are needed to enhance knowledge about breast cancer and facilitate timely diagnoses.

Keywords Stage at diagnosis · Breast neoplasms · Delay · Ethiopia

Introduction

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women worldwide, with about 2,088,849 new cancer cases and 626,679 deaths

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occurred in 2018 [1]. Similarly, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women in Ethiopia, with an estimated 15,244 newly diagnosed cases and 8159 deaths in 2018 [2]. These numbers are expected to substantially increase because of the aging and growth of the population, as well as changes in reproductive factors. The fertility rate in Addis Ababa, the capital city of Ethiopia, is now less than two live births per woman [3], comparable to those from European countries. Survival after diagnosis of breast cancer is poor in Ethiopia [4, 5] because of late-stage at diagnosis [4, 6] and limited access to standard treatments [7].

In settings like Ethiopia with no national or regional breast cancer early detection program, early-stage diagnosis could be achieved by shortening the time intervals from breast symptoms recognition to diagnosis of symptomatic breast cancer patients [8–10]. These intervals include patient interval (time interval in seeking medical care after recognition of first breast cancer symptoms) and diagnostic interval (time interval between initial medical consultation and diagnostic confirmation) [11, 12]. The association between patient or diagnostic interval and stage at diagnosis is not consistently demonstrated across studies [8, 10, 13, 14]. Also, to our knowledge, no previous study examined the distribution of stage at diagnosis and factors associated with advanced stage at diagnosis for breast cancer in Ethiopia. In this study, we examined the stage distribution of breast cancer among women and factors associated with advanced stage at diagnosis based on newly diagnosed breast cancer patients seen in seven major health facilities, capturing 90% of breast cancer cases recorded in Addis Ababa population-based cancer registry.

Methods

Data for this study were obtained from an ongoing follow-up study in Addis Ababa [15] documenting the experience of 441 women diagnosed with invasive breast cancer, from recognition of symptoms to diagnosis, treatment, and survivorship and end of life. Study details are described elsewhere [16]. Briefly, study participants were recruited from January 1, 2017 to June 30, 2018 consecutively from 7 major health facilities in Addis Ababa. Participants were 18 years and above, residents of Addis Ababa (residing in Addis Ababa for at least 6 months before diagnosis), and non-recurrent cases of breast cancer. The seven major health facilities capture 90% of breast cancer cases recorded in the Addis Ababa population-based cancer registry, which was established in 2011 [17] and is a member of the Africa Cancer Registry Network.

Stage at diagnosis, the primary outcome of this study, was abstracted from patient medical charts and classified into clinical stage I, II, III, and IV according to clinical characteristics (physical examinations, ultrasound, chest X-ray, CT-Scan, and magnetic resonance imaging) because of lack of information on tumor characteristics from pathology reports [18]. Stages were further grouped into early stages (I and II) and advanced stages (III and IV) [14, 19]. Also abstracted from medical charts were date of histopathologic confirmation, histologic tumor type, grade, hormone receptor status, human epidermal growth factor 2, surgical margin involvement, lymphovascular invasion, and tumor size.

A face to face structured interviewer-administered questionnaire was applied to study participants during study recruitment to obtain information on exposure variables, including age at diagnosis, marital status, education status, job, family monthly income, source of medical expenses, ever practiced breast self-examination before symptoms recognition, types of symptoms first recognized, types of health facility first consulted, number of health facilities visited before diagnosis, traditional medicine use before confirmation, and date of first symptom(s) recognition. If participants, however, were unable to recall the exact date of first symptom(s) recognition, they were asked to provide the month, or the year ("was it at the beginning, middle, or end of the year?"). For those who remembered only the month, the date was estimated as the 15th day of that month. If the participants remembered only the beginning, middle or end of the year, the estimated date was assigned as the 15th of February, June 15, or October 15 of that year, respectively. For those who were only able to provide the year, the estimated date was June 30th of that year.

The time intervals experienced from symptom recognition to diagnostic confirmation were categorized as patient interval (from the date of first recognition of symptoms to the date of first clinical presentation) or diagnostic interval (from the date of first clinical presentation to the date of pathologic confirmation) [11]. This classification, however, ignores the complex interaction between patient, societal, and health system factors that contribute to both types of delay [20]. For example, patient-related factors such as belief in traditional medicine, fear of cancer diagnosis and treatment, refusal of breast removal, inability to take time off from work, and financial barriers could contribute to both patient and diagnostic intervals [16]. Therefore, we also calculated total time interval, the time interval from date of first symptom recognition to date of pathologic confirmation [21, 22]. Patient, diagnostic, and total time intervals were considered delayed if the intervals were > 3 months, > 2 months, and > 6 months, respectively.

Statistical analysis

The primary outcome, stage at diagnosis, was dichotomized into a binary outcome variable indicating early-stage coded

as "0" and advanced stage coded as "1". In cross-sectional studies with binary outcomes, logistic regression is commonly used to estimate odds ratio (OR) as a measure of association equivalent to the relative risk (RR). However, when the outcome is common (> 10%), the OR overestimates the RR and makes interpretation of findings difficult. In such cases, prevalence ratio (PR) is a recommended measure of association [23, 24]. Poisson regression with robust variance rather than logistic regression helps to directly estimate PR and facilitate the interpretation of results as prevalence ratios rather than ORs [25]. Factors that were associated with advanced stage at diagnosis in the bivariate analysis at p-value < 0.25 [26] were retained in the multivariable analysis and adjusted prevalence ratio (aPR) reported. Statistical significance was declared at p-value < 0.05, two-sided. In a supplementary analysis, we similarly examined factors associated with early-stage diagnosis as early-stage diagnosis is also common. The final analysis was based on 406 patients with known stage information.

Results

The socio-demographic characteristics of the study participants have been previously described [16]. The mean (standard deviation) age at diagnosis was 44.4 (12.2) years.

Table 1 describes tumor characteristics. The majority (83.7%) of the cases were ductal carcinoma. Among the 48 patients with known hormone receptor status, 33 (68.8%) were hormone receptor-positive (ER- and/or PR-positive), ten patients had triple-negative breast tumor. Tumor grade was poorly differentiated for one-fifth of the patients. Taking the largest dimension of the tumor, the median (interquartile range) tumor size at presentation was 4 (3 to 6) centimeters. Two-thirds of the patients (64.3%; 95% CI 59.5%, 68.8%) were diagnosed at advanced stages (III and IV) of their disease, with nearly one-third (30.7%) metastasized, primarily to liver, lung and bone. Only 13.1% of the patients were diagnosed at stage I (Table 1).

Factors associated with advanced stage at diagnosis

In the multivariable analysis, the prevalence of advanced stage at diagnosis was significantly higher among women who used traditional medicine before diagnostic confirmation (aPR = 1.29; $p = 0.002$). In contrast, the prevalence of advanced stage at diagnosis was lower among women who practiced breast self-examination before symptom recognition (51.1%) compared to those who did not (67.9%) (aPR = 0.77; $p = 0.021$) (Table 2).

In the adjusted model, both patient delay of > 3 months (aPR = 1.16; $p = 0.042$) and diagnosis delay of > 2 months (aPR = 1.24; $p = 0.004$) were statistically significantly associated with higher prevalence of advanced stage at diagnosis (Table 2). Also, delay > 6 months in diagnostic confirmation from date of first symptom(s) was significantly associated with higher prevalence of advanced stage diagnosis compared to those who received diagnostic confirmation within 3 months from date of recognition of first symptoms (71.2% vs 51.6%, aPR = 1.35; $p = 0.002$) (Table 3). In a sensitivity analysis, exclusion of patients who did not remember the day or month of first symptom recognition did not alter the findings on the association between delays and advanced stage at diagnosis (data not shown). In a supplementary analysis, factors associated with early-stage at diagnosis were similar to those of advanced stage at diagnosis, and as expected in the opposite directions (Supplementary Table 1).

Discussions

In this study of female breast cancer in Addis Ababa city, we found a high prevalence of advanced stage diagnoses. Sixty-four percent of the patients were diagnosed at advanced stage of their disease, with 19.7% metastatic disease at initial presentation. Use of traditional medicine before diagnosis, patient delay of > 3 months following date of recognition of breast symptom, and diagnosis delay of > 2 months following date of medical consultation for breast symptom were significantly associated with increased prevalence of advanced stage at diagnosis. In contrast, practicing breast self-examination before symptom recognition was associated with decreased prevalence of advanced stage at diagnosis. The factors associated with early-stage at diagnosis were the same as those of advanced stage at diagnosis, except the directions of the associations were reversed.

In our study, the prevalence of advanced stage at diagnosis as expected was significantly lower than that found in the rural part of Ethiopia (85%) [27] and slightly higher than that seen in a study conducted in one private clinic in Addis Ababa (55%) [28]. The variation could be due to differences in the study participants' socio-economic status and access to health information and health facilities. Our estimate was generally comparable with population-based estimate for sub-Saharan Africa (64.9%) [19] but as expected significantly higher than those from countries outside of sub-Saharan Africa such as Iran (36.2%) [22] and USA (26.6%) [29].

Stage at diagnosis is an important independent factor determining the choice of treatment, health-related quality of life, and survival [30] for breast cancer. Women diagnosed at advanced stage of the disease usually receive palliative therapy and have poorer prognosis than those diagnosed at early-stage [31]. For instance, Maajani et al. reported that 5-year survival was nearly threefold lower among women diagnosed at stage IV (32.0%) compared to those diagnosed at stage I (86.0%) [30]. In addition, late-stage tumors are

Table 1 Tumor characteristics of women with breast cancer diagnosed from 2017 to 2018 Addis Ababa city, Ethiopia ($n=406$)

Characteristics	Frequency	Percentage
Histological tumor type		
Ductal	340	83.7
Lobular	13	3.2
Mixed	16	4.0
Others	36	8.9
Not specified	1	0.2
Receptor status specified		
Yes	48	11.8
No	357	88.2
Hormone receptor status ($n=48$)		
ER and PR-positive	20	41.7
ER-positive and PR-negative	9	18.7
PR-positive and ER-negative	4	8.3
ER and PR-negative	15	31.3
Human epidermal growth factor 2 status ($n=35$)		
Positive	8	22.9
Negative	26	74.3
Equivocal	1	2.8
Histological grade		
Well-differentiated (Grade 1)	52	12.8
Moderately differentiated (Grade 2)	123	30.3
Poorly differentiated (Grade 3)	82	20.2
Not specified	149	36.7
Surgical margin status ($n=308$)[a]		
Negative	205	66.6
Positive	48	15.6
Not specified	55	17.8
Lymphovascular invasion ($n=308$)[a]		
Negative	27	8.8
Positive	30	9.7
Not specified	251	81.5
Tumor size at presentation (in greatest dimension)		
≤2 cm	44	10.8
>2–5 cm	165	40.6
>5 cm	100	24.6
Not specified	97	23.9
Group stage at diagnosis		
I	19	4.7
II	126	31.0
III	181	44.6
IV	80	19.7

[a]Results shown only for patients with documentation of stage ≤ III and surgery in the pathology report or medical chart of the patients

ER Estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor 2

more difficult and costly to treat than early-stage tumors [32]. The morbidity and mortality and the associated economic burden of advanced stage at diagnosis are more prominent in sub-Saharan African countries because of limited early detection services and treatment centers [30]. Similar to other sub-Saharan African countries, in Ethiopia, advanced stage at diagnosis of breast cancer contributes to poor health-related quality of life [33], and associated with poor survival [5, 6, 12] and increased burden on the existing limited cancer treatment centers in the country [7, 34]. Thus,

Table 2 Factors associated with advanced stage (III and IV) at diagnosis among women with breast cancer diagnosed from 2017 to 2018 Addis Ababa city, Ethiopia

Patient characteristics	Advanced stage at diagnosis		Unadjusted		Adjusted	
	No	Yes	PR (95% CI)	*p*-value	aPR (95% CI)	*p*-value
Age at diagnosis					NI	
< 40	64 (36.8%)	110 (63.2%)	Ref			
40–59	58 (34.1%)	112 (65.9%)	1.04 (0.89, 1.22)	0.606		
≥ 60	23 (37.1%)	39 (62.9%)	0.99 (0.79, 1.24)	0.965		
Women's education					NI	
Not attended school	28 (34.6%)	53 (65.4%)	1.08 (0.85, 1.35)	0.521		
Primary school	36 (35.0%)	67 (65.0%)	1.07 (0.86, 1.33)	0.534		
Secondary school	46 (34.6%)	87 (65.4%)	1.07 (0.87, 1.32)	0.479		
Diploma and above	35 (39.3%)	54 (60.7%)	Ref			
Marital status						
Married	89 (37.9%)	146 (62.1%)	0.92 (0.79, 1.06)	0.283	NI	
Single, widowed or divorced	56 (32.7%)	115 (67.3%)	Ref			
Had outdoor job					NI	
No	75 (33.3%)	150 (66.7%)	Ref			
Yes	70 (38.7%)	111 (61.3%)	0.92 (0.79, 1.07)	0.270		
Family monthly income						
< 61.0[a]	38 (31.2%)	84 (68.8%)	1.15 (0.94, 1.41)	0.172	1.05 (0.85, 1.30)	0.648
61.0–194.0[$]	68 (36.4%)	119 (63.6%)	1.06 (0.87, 1.29)	0.534	1.00 (0.83, 1.22)	0.933
> 194.0[$]	39 (40.2%)	58 (59.8%)	Ref		Ref	
Source of medical expenses					NI	
Out of pocket	104 (36.2%)	183 (63.8%)	0.91 (0.67, 1.23)	0.542		
Free medical care	35 (33.3%)	64 (64.7%)	0.92 (0.67, 1.27)	0.628		
Health insurance	6 (30.0%)	14 (70.0%)	Ref			
Practiced BSE[a]						
No	102 (32.1%)	216 (67.9%)	Ref		Ref	
Yes	43 (48.9%)	45 (51.1%)	0.75 (0.60, 0.93)	0.011	0.77 (0.63, 0.96)	0.021*
Breast pain as first symptom					NI	
No	132 (36.2%)	233 (63.8%)	Ref			
Yes	13 (31.7%)	28 (68.3%)	1.07 (0.86, 1.34)	0.552		
Painless lump as first symptom						
No	26 (30.6%)	59 (69.4%)	Ref			
Yes	119 (37.1%)	202 (62.9%)	0.90 (0.77, 1.07)	0.242	0.87 (0.74, 1.02)	0.088
Traditional medicine use[b]						
No	77 (46.9%)	87 (53.1%)	Ref		Ref	
Yes	68 (28.1%)	174 (71.9%)	1.35 (1.15, 1.59)	0.000	1.29 (1.10, 1.52)	0.001*
Patient delay (> 3 months)						
No	106 (39.9%)	160 (60.1%)	Ref		Ref	
Yes	39 (27.9%)	101 (72.1%)	1.19 (1.04, 1.38)	0.012	1.16 (1.00, 1.34)	0.042*
Diagnosis delay (> 2 months)						
No	80 (43.5%)	104 (56.5%)	Ref		Ref	
Yes	65 (29.3%)	157 (70.7%)	1.25 (1.07, 1.45)	0.004	1.24 (1.07, 1.43)	0.004*
First medical consultation						
Public health center	51 (35.2%)	94 (64.8%)	1.06 (0.89, 1.26)	0.468	0.96 (0.80, 1.16)	0.670
Public hospital	29 (30.5%)	66 (69.5%)	1.14 (0.95, 1.37)	0.151	1.05 (0.88, 1.26)	0.565
Private hospital/clinic	65 (39.2%)	101 (60.8%)	Ref		Ref	
Number of health facilities visited before diagnosis					NI	
≤ 3	112 (36.5%)	195 (63.5%)	Ref			
≥ 4	33 (33.3%)	66 (66.7%)	1.05 (0.89, 1.23)	0.561		

aPR adjusted prevalence ratio, *BSE* breast self-examination, *NI* not included in the multivariable model

[$]US dollar, *significant factors

Table 2 (continued)

[a]Before symptom recognition; [b]before diagnostic confirmation

Table 3 Association between total delay (symptom duration) and advanced stage (III and IV) at diagnosis among women with breast cancer diagnosed from 2017 to 2018 Addis Ababa city, Ethiopia

Patient characteristics	Advanced stage at diagnosis		Unadjusted		Adjusted*	
	No	Yes	PR (95% CI)	*p*-value	aPR (95% CI)	*p*-value
Total delay (symptom duration)						
< 3 months	62 (48.4%)	66 (51.6%)	Ref		Ref	
3–6 months	26 (35.1%)	48 (64.9%)	1.26 (0.99, 1.59)	0.058	1.23 (0.97, 1.56)	0.075
> 6 months	57 (27.9%)	147 (72.1%)	1.40 (1.15, 1.68)	0.001	1.35 (1.12, 1.63)	0.002

*Adjusted to the variables in Table 2

downstaging of breast cancer in Ethiopia and other resource-limited settings helps not only cancer patients and their families but also governments by decreasing costs associated with morbidity, premature mortality, and productivity loss.

Downstaging of breast cancer could be achieved through implementation of interventions to reduce known risk factors such as knowledge deficits [35], traditional medicine use [36], and being uninsured [37]. We found that traditional medicine use before diagnosis was statistically significantly associated with advanced stage at diagnosis. According to different pocket studies, the prevalence of traditional medicine use in Ethiopia ranged from 61 to 71% [38, 39]. Another study conducted in Addis Ababa, the capital city of Ethiopia, documented that cancer patients were among the most common visitors to traditional healers in the city [40]. Reasons for use of traditional medicine include difficulties in accessibility and affordability of modern medicine, dissatisfaction with modern medicine, and the acceptability of traditional medicine in their community [39, 40]. The time elapsed while practicing traditional medicine may have contributed to the progression of the disease before diagnosis. Akhtar et al. reported that women in Bangladesh on average waited 3 months using traditional medicines before making medical consultation and there was a positive correlation between traditional medicine use and delayed diagnosis [36]. Therefore, there is a need to involve traditional healers in breast health education to reduce diagnostic delay and promote early detection and downstaging of the disease in Ethiopia and other economically developing countries.

Our findings of statistically significant higher prevalence of advanced stage at diagnosis among women who had patient and diagnosis delays are consistent with previous reports [8, 21, 22]. The association of diagnosis delay with advanced stage at diagnosis was more overt than patient delay. Reasons for delayed diagnosis include both provider and patient factors such as misdiagnosis, false-negative laboratory results, traditional medicine use, fear of diagnosis, and financial barriers [16]. Therefore, interventions to improve patient and provider knowledge about breast cancer in the country may shorten delays in diagnostic confirmation.

We found that women who had practiced breast self-examination before symptom recognition had lower prevalence of advanced stage at diagnosis. Women who practiced breast self-examination are likely to be more knowledgeable about breast cancer and to seek care earlier than their counterparts. Moreover, previous studies in Ethiopia and other parts of Africa reported significant association between breast cancer knowledge before symptom recognition and advanced stage at diagnosis [16, 21, 41–44].

Breast cancer in Addis Ababa has significant public health and societal implications given the majority of the cases are diagnosed at advanced stage, and half of the cases occur in women aged 41 or lower when they are raising children and supporting other family members. The proportion of patients diagnosed with advanced stage disease is likely to be considerably higher in other parts of the country than in Addis Ababa as health literacy level and access to health are inferior. For instance, Deressa et al. [27] found that 85% of women with breast cancer in Northern Ethiopia diagnosed at advanced stage compared to 64.3% in Addis Ababa.

Our findings of the association between advanced stage diagnosis and traditional medicine use before diagnostic confirmation, patient delay, and diagnosis delay in Addis Ababa suggest that late-stage diagnosis in the city may be downstaged by enhancing public awareness about breast cancer signs and symptoms and the importance of regular breast self-examination for breast abnormalities through public campaigns and programs for breast cancer. There is also a need for implementing continuing education on breast health for front-line health workers for prompt referral of women with breast abnormalities for timely diagnostic confirmation [45].

The strength of our study is the use of population-based data to examine the association between advanced stage at

diagnosis of breast cancer with patient and diagnostic delay in African setting. Our study has several limitations, however. First, the proportion of late-stage at diagnosis was computed from those with known stage and those who sought medical care. However, stage at diagnosis was missing for only 35 patients (7.9%), and there was no significant difference in the socio-demographic and clinical characteristics between patients with known and unknown stage. Second, our analysis was based on clinical staging rather than pathologic staging because nodal status in pathology report was missing for the majority of patients [18]. Clinical staging, however, likely provides a good approximation of pathological staging in Ethiopian settings as most patients are diagnosed at advanced stage of the disease [46]. Third, dates of first symptom recognition and of first medical consultation may have introduced recall bias but they are unlikely to differ by stage at diagnosis. Further, the associations between advanced stage at diagnosis and patient delay and diagnostic delay remained unchanged when women who did not remember the exact day or month of first symptom(s) recognition excluded from analysis.

Conclusions

About two-thirds of women with breast cancer in Addis Ababa, the capital city of Ethiopia, were diagnosed with advanced stage disease, which was strongly associated with breast self-examination, with traditional medicine use, with patient delay and diagnosis delay. These findings underscore the need to enhance community and healthcare provider awareness about the importance of early presentation following breast symptoms and prompt referral following medical consultation for suspicious breast abnormalities.

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Data availability The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board of College of Health Science of Addis Ababa University (018/17/SPH), and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Paper-IV

Effect of delay in breast cancer diagnosis on survival of women with breast cancer in Addis Ababa, Ethiopia: A prospective cohort study

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Abstract

Background: There are limited data on the association between delay in breast cancer diagnosis following breast symptoms recognition and survival, particularly in Africa. Herein, we examined whether delay in breast cancer diagnosis is associated with overall survival among women in Addis Ababa, Ethiopia.

Methods: A total of 441 women diagnosed with breast cancer from 01 January 2017 to 30 June 2018 in Addis Ababa were followed for survival to the end of 2019. Survival rates were estimated using Kaplan Meier. The association between delay in diagnosis (>3 months following symptoms recognition) and overall survival was computed using multivariable Cox regression model adjusting for demographic and clinical factors.

Results: During a median follow-up period of 25.1 months, two-year overall survival rate was 73.5% (95% CI: 68.0%, 78.2%) in women with diagnosis delay compared to 79.1% (95% CI: 71.2%, 85.1%) in those women without diagnosis delay. In the multivariable Cox regression model, the risk of death was 87% higher (HR=1.87, 95% CI [1.15, 3.03]) in women with compared without diagnosis delay. Also, women diagnosed at stage I had a 2-years survival of 100% in contrast to 26.7% at stage IV. The risk of death was significantly higher among women diagnosed with advanced-stages (HR=3.32, 95% CI [1.81, 6.10]).

Conclusions: Only 3 in 4 women with breast cancer in Addis Ababa survived 2 years following their diagnosis. Delay in diagnostic confirmation of breast cancer following recognition of breast symptoms was negatively associated with overall survival in Addis Ababa, Ethiopia, underscoring the need to increase awareness about the importance of prompt presentation for clinical evaluation and referral for diagnostic confirmation to mitigate the undue high burden of the disease in the country and other parts of Africa.

Keywords: Breast Cancer, Neoplasm, Carcinoma, Delay, survival, Addis Ababa, Ethiopia

Introduction

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women in most parts of the world [1-6]. The survival rate is lower in resource-limited countries like sub-Saharan Africa than in developed countries [7] because of lack of early detection or screening strategy, detection of the disease at a late stage, limited treatment options, and molecular and genetic characteristics of the tumor [2, 3, 7-11]. In Ethiopia, nearly half of the women with breast cancer (47.0%) died within two years of diagnosis [8]. Most breast cancer deaths are occurring at a young age [8] when women are raising a family and supporting other family members.

The association between delayed diagnosis following symptom recognition and survival of women with breast cancer is not consistently demonstrated [9-15]. For instance, these studies assessed the effect of either patient or diagnostic interval on survival. However, the interval from symptom recognition to diagnosis (symptom interval) [16] matters since the underlining causes of patient and diagnosis delay are intertwined. Also, most of the studies addressing the relationship between patient/diagnosis delay and survival were retrospective, and prone to data incompleteness and recall bias of the dates of symptom recognition, first medical consultation, and confirmation. To solve the controversial relationship, a prospective study assessing the effect of symptom interval on breast cancer survival is essential. Here in, we investigated the association between delayed diagnosis following symptom recognition and survival of women with breast cancer using a prospective cohort study.

Methods

Study details have been published previously [17]. Briefly, a prospective cohort study was conducted among 441 women diagnosed with primary invasive breast cancer from January 2017 to June 2018 in seven health facilities of Addis Ababa city, where >90% of the breast cancer cases are seen. The study was ethically approved by the Institutional Review Board (018/17/SPH) of the College of Health Science of Addis Ababa University, and verbal consent was obtained from the study participants.

The primary exposure variable was symptom interval, which is the time interval from recognizing the first symptom(s) to date of breast cancer diagnosis [16]. The date of first

symptom recognition was obtained from face-to-face interviews with the women during the recruitment time, while date of diagnosis was obtained from the patients' medical charts. Symptom interval was dichotomized into <3 months and >3 months [10]. Socio-demographic characteristics of the patients such age at diagnosis, marital status, women's educational status, women's occupation, family monthly income, and traditional medicine use before confirmation were obtained from face-to-face interviews with the women during the recruitment time.

We categorized age into <40 years, 40-59 years, and $\geq$ 60 years; educational attainment into not attended formal school, primary school (grade 1-8), secondary school (grade 9-12), and some level of college education (>12 years of schooling); marital status into married and unmarried (single, widowed or divorced); family monthly income categorized into <61.0 USD, 61.0 - 194.0 USD, and >194.0 USD. Traditional medicine use was considered "yes" if the women used holy water, visited traditional healers, or performed any ritual activities to treat breast cancer before diagnosis.

Also, clinical explanatory variables, such as stage at diagnosis, documented co-morbidities at diagnosis, receipt of surgical treatment, delay to adjuvant chemotherapy initiation (the interval between definitive breast cancer surgery and initiation of adjuvant chemotherapy), receipt of radiation therapy, and hormonal therapy, histologic tumor grade, and receptor subtype, were systematically extracted from the medical charts of the patients. Extraction was done about one year after diagnosis by trained oncology residents and updated at the end of the follow-up. Stage was categorized according to the 7^{th} edition of the American Joint Committee on Cancer (AJCC) [18] and dichotomized into early stage (stages I and II) and advanced stage (Stages III and IV). Comorbidities was categorized into absent (0) or present (> = 1); breast surgery into "yes" or "no"; hormonal therapy into "yes" or "no".

The study's primary outcome was death from all causes and was obtained either from the patients' medical chart or through a phone call to the patients' next of kin. The study participants were followed from the date of diagnosis with invasive breast cancer until the date of the last contact, the date of death or until the end of the study (31 December 2019), whichever occurred first. The last status determination was done at about two years after the recruitment of the study participants. All participants or their next of kin were contacted using their telephone number or

that of their relatives, which was recorded during recruitment to the follow-up study, to collect data about the receipt of treatments and eventual date of death. Participants who remained alive at the date of the last follow-up (31 December 2019) were censored.

Two of the women have no valid follow-up and treatment related data, and we excluded them from the analysis. Hence, in this analysis, we have included 439 women with breast cancer. Two women were lost to follow-up after 16 months and 17 months follow-up, respectively, and were censored for the one-year survival but considered lost to follow-up for the two-year survival estimation. The overall survival was computed in months from date of diagnosis to death from all causes [19-21]. Also, a sensitivity analysis was done by calculating the overall survival from the date of first symptoms (includes breast lump, pain, discharge, color change, or numbness) recognition to death.

Statistical analysis was performed using Stata version 13 software. Two-year overall survival rate was estimated using the Kaplan-Meier method and compared using the log-rank test. In addition, multivariable Cox proportional hazards model was run to compute the adjusted hazard ratio of each of the predictors in the model. Variables with a p-value of < 0.25 on bivariate analyses were entered into the multivariable model. Proportional hazards assumption was checked using the graphical method and goodness of fit test, which were all satisfied. All statistical tests were two-sided, and a p-value of < 0.05 was considered statistically significant.

Results

The mean age was 44.4 years (Standard deviation=12.2 years). Of the 441 women with breast cancer enrolled in the follow-up, two were lost to follow-up and had no treatment-related data. Table 1 describes the treatment status of the 439 study participants. Seventy-nine percent of the women received surgical treatment predominately mastectomy.

Table 1: Treatment status of women diagnosed with breast cancer from 1 January 2017 to 30 June 2018 in Addis Ababa city, Ethiopia (n=439)

Characteristics	Frequency	Percentage
Surgical therapy done (n=439)		
Yes	348	79.3
No	75	17.1
Unspecified	16	3.6
Type of surgery done (n=348)		

Mastectomy	320	92.0
Lumpectomy	7	2.0
Unspecified	21	6.0
Chemotherapy received (n=439)		
Yes	374	85.2
No	45	10.3
Unspecified	20	4.5
Timing of chemotherapy treatment (n=374)		
Neoadjuvant	28	7.5
Adjuvant	260	69.5
Unspecified	86	23.0
Type of chemotherapy (n=374)		
Anthracycline based only (AC, FAC, FEC)	103	27.5
Anthracycline + taxane (AC-T/ EC-T)	227	60.7
Cyclophosphamide/methotrexate/fluorouracil (CMF)	6	1.6
Docetaxel and cyclophosphamide (TC)	3	0.8
Taxol	3	0.8
Dacarbazine and Adriamycin	1	0.3
Unspecified	31	8.3
Delay to initiation of adjuvant chemotherapy (n=223)		
≤ 30 days	42	18.8
31-60 days	65	29.2
61-90 days	48	21.5
>90 days	68	30.5
Radiotherapy received (n=439)		
Yes	137	31.2
No	277	63.1
Unspecified	25	5.7
Aim of the radiotherapy (n=137)		
Adjuvant	88	64.2
Palliative	33	24.1
Unspecified	16	11.7
Adjuvant radiotherapy waiting intervals (n=57)		
≤ 30 days	7	12.3
31-60 days	13	22.8
61-90 days	5	8.8
>90 days	32	56.1
Hormonal therapy received (n=439)		
Yes	325	74.0
No	88	20.0
Unspecified	26	6.0

The median follow-up time, calculated from the diagnosis date, was 25.1 months (IQR: 19.3 to 31.4 months). By the end of the follow-up, 128 women died, making the cumulative incidence of death 29.2% (95% CI [25.0%, 33.6%]). Forty-percent (n=51) of the deaths happened within one year of diagnosis. The overall mortality rate over the 864.5 person-years follow-up was 148.0 deaths per 1000 person-years (95% CI [124.0, 176.0]).

Figure 1 shows the overall survival rate computed from date of diagnosis to the end of the follow-up. The overall one- and two-year survival rate was 88.3% (95% CI [84.9%, 91.0%) and 75.2% (95% CI [70.7%, 79.0%]), respectively.

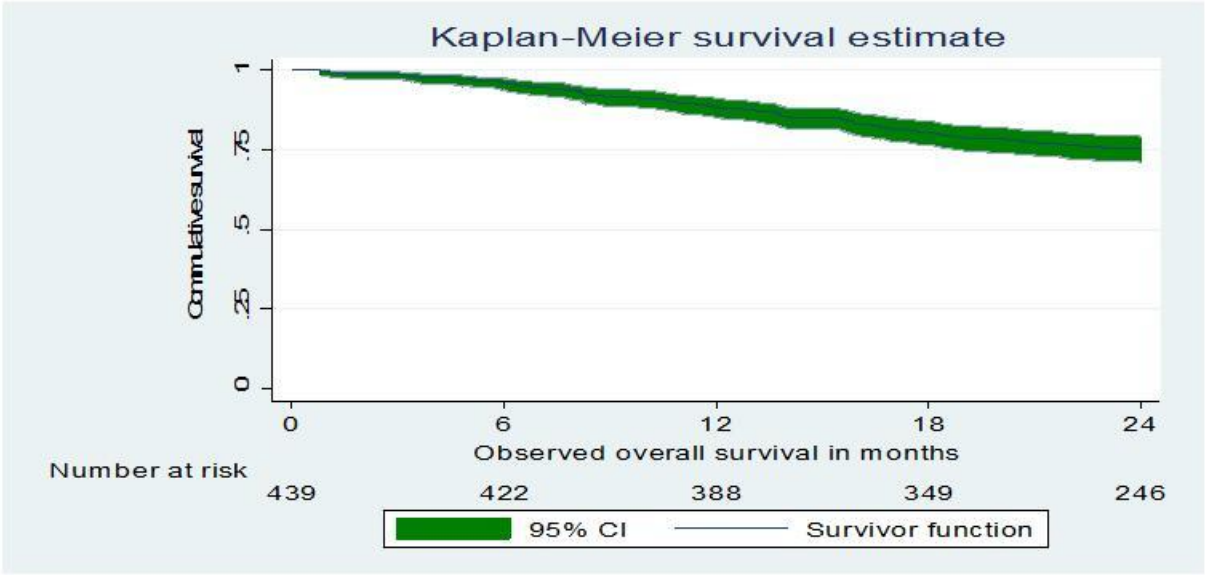

Figure 1: Overall survival rate of women with breast cancer diagnosed from 1 January 2017-30 June 2018 in Addis Ababa city, Ethiopia (Survival computed from date of diagnosis)

When the survival rate is computed from the date of first symptom recognition to the end of the study, the median follow-up was 33.8 months (IQR: 25.8 to 40.2). Over the 1411.6 person-years follow-up, the rate of death was 90.7/1000 person-years (95% CI [76.2, 107.8]). The one- and two-year overall survival rates were 96.3% (95% CI [94.0%, 97.7%]) and 85.0% (95% CI [81.3%, 88.1%]), respectively (Figure 2).

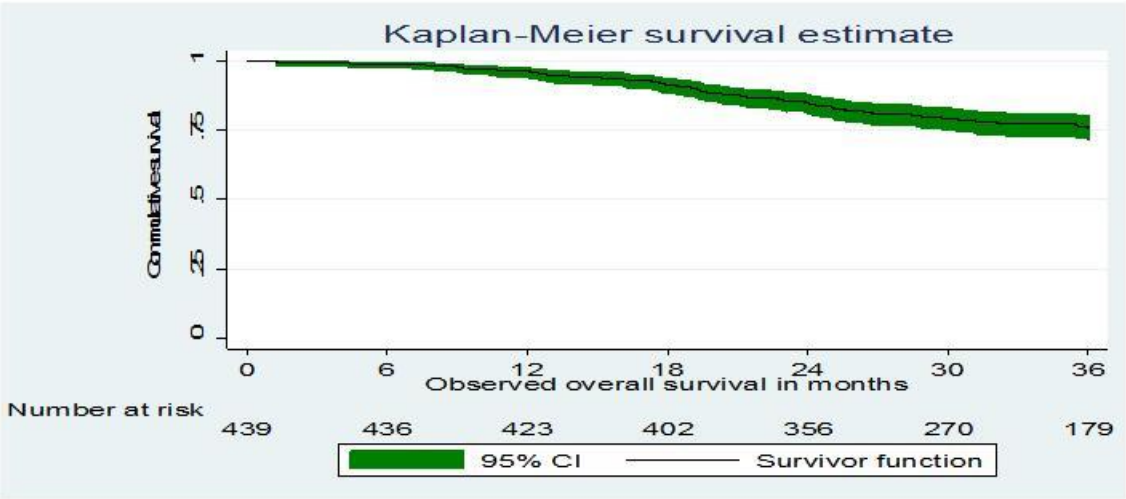

Figure 2: Overall survival rate of women with breast cancer diagnosed from 1 January 2017-30 June 2018 in Addis Ababa city, Ethiopia. (Survival computed from date of symptom recognition)

The survival rate was significantly lower among women diagnosed with advanced-stage (Table 2 and Figure 3). The one- and two-year overall survival rate of women diagnosed at stage I was 100%, while for stage IV was 62.0% and 26.7%, respectively (Table 3). In the multivariable analysis, stage at diagnosis was the strongest predictor of women's 2-year overall survival. Women diagnosed at advanced-stage had about 4 fold increased risk of death (HR=3.32, 95% CI [1.81, 6.10]) compared to those diagnosed at early stage (Table 3).

Table 2. Overall one- and two-year survival rate of women with breast cancer by stage at diagnosis in Addis Ababa city, Ethiopia

Stage at diagnosis	**One-year overall survival rate (95% CI)**	**Two-year overall survival rate (95% CI)**
Stage I	100.0%	100.0%
Stage II	96.0% (90.7%, 98.3%)	90.9% (84.2%, 94.9%)
Stage III	92.7% (87.9%, 95.7%)	80.8% (74.3%, 85.9%)
Stage IV	62.0% (50.4%, 71.7%)	26.7% (16.8%, 37.6%)

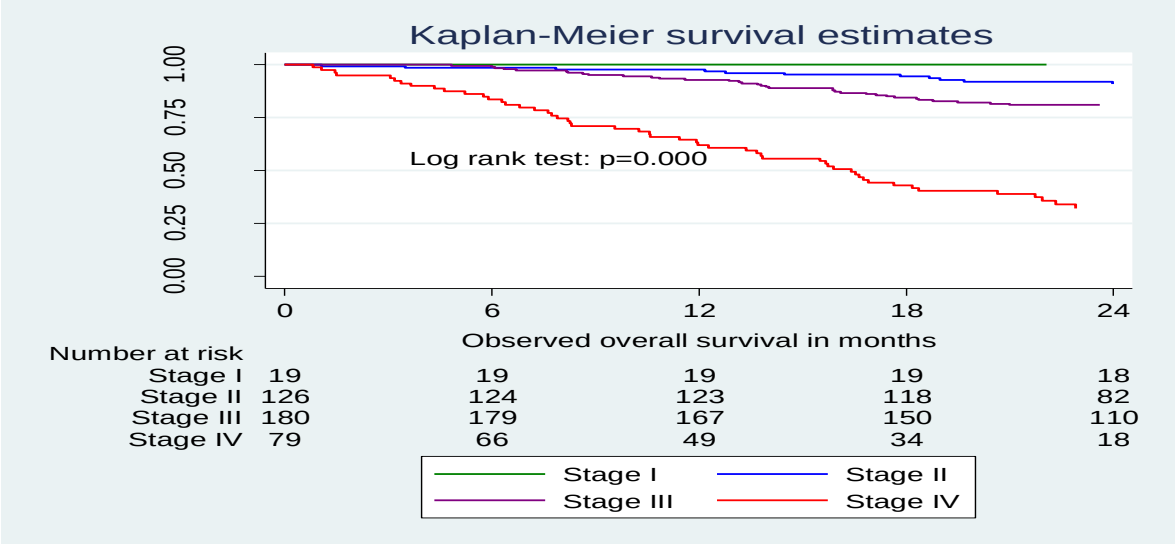

Figure 3: Overall survival rate of women with breast cancer diagnosed from 1 January 2017-30 June 2018 by stage at diagnosis in Addis Ababa city, Ethiopia

In addition to the stage at diagnosis, overall survival was lower among women who had symptom interval of >3 months (Figure 4). The two-year overall survival rate of women

diagnosed within 3 months of symptom recognition was 79.1% (95% CI: 71.2%, 85.1%), while for those diagnosed after 3 months of symptom recognition was 73.5% (95% CI: 68.0%, 78.2%). After adjusting for stage at diagnosis and other variables in Table 14, delayed confirmation following symptom recognition was significantly associated with increased risk of death. Women who waited for >3 months before confirmation (HR=1.87, 95% CI [1.15, 3.03]) had 87% higher risk of death compared to these diagnosed within 3 months of symptom recognition (Table 3).

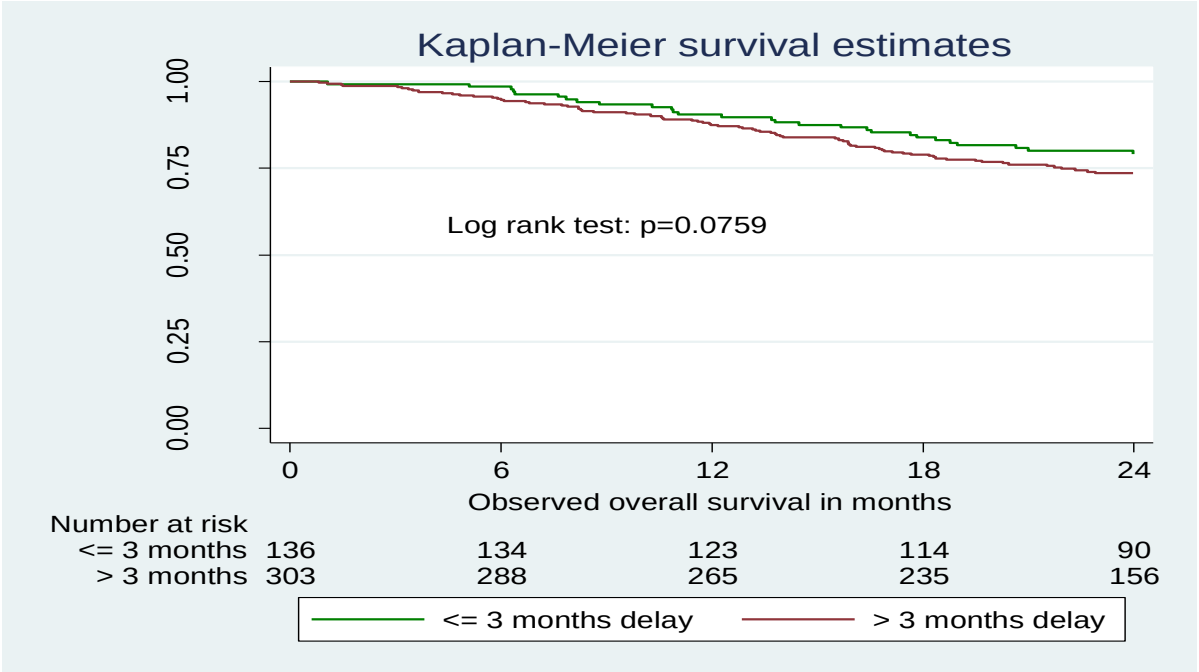

Figure 4: Overall survival rate of women with breast cancer diagnosed from 1 January 2017-30 June 2018 by symptom interval in Addis Ababa city, Ethiopia.

After controlling to stage at diagnosis and other variables in table 2, having surgical therapy (HR=0.23, 95% CI [0.15, 0.35]) and hormonal therapy (HR=0.26, 95% CI [0.17, 0.40]) had a protective effect on survival of women with breast cancer (Table 3).

Age at diagnosis of ≥ 60 years (HR=1.84, 95% CI [1.13, 2.99) was significantly associated with increased risk of death. The association was, however, attenuated after adjusted to other variables in the model. Similarly, other socio-demographic variables: being unmarried at the time of diagnosis (HR=1.43, 95% CI [1.01, 2.03]), and having lower family monthly income (HR=1.68, 95% CI [1.04, 2.71]) were significantly associated with increased risk of death. Conversely, the risk of death was significantly lower among women having a diploma and above education

(HR=0.43, 95% CI [0.24, 0.75]) than those who did not attend school. This association was also not maintained after adjustment.

Partner education was also negatively associated with death. Women with partner educational level of secondary school (HR=0.46, 95% CI [0.22, 0.97]) or diploma and above (HR=0.29, 95% CI [0.13, 0.63]) were at lower risk of death compared to those who did not attend school. But, to keep our model's power, we did not include partner education into the multivariable model (Table 3).

Though the significant association was attenuated in the multivariable analysis, on bivariate analysis, the risk of death was higher among women who ever used traditional medicine before diagnosis (HR=1.89, 95% CI [1.28, 2.80]), and women with grad 3 (poorly differentiated) tumors (HR=2.19, 95% CI [1.03, 4.67]), and women having hemoglobin level of <12 g/dl at diagnosis (HR=1.96, 95% CI [1.19, 3.23]) but lower among women who had practiced breast self-examination before symptom recognition (HR=0.44, 95% CI [0.26, 0.74]) (Table 3).

Table 3: Bivariate and multivariable Cox regression analysis of factors affecting overall survival of women with breast cancer diagnosed from 1 January 2017 to 30 June 2018 in Addis Ababa city, Ethiopia

Variables	Status at last contact		Bivariate Cox regression		Multivariable Cox regression
	Censored (%)	Death (%)	HR (95% CI)	P-value	HR (95% CI)
Age at diagnosis (years)					
<40	138(75.8)	44(24.2)	Ref.		Ref.
40-59	129(69.0)	58(31.0)	1.33(0.90, 1.97)	0.146	1.34(0.83, 2.16)
≥60	42(61.8)	26(38.2)	1.84(1.13, 2.99)	0.014	1.18(0.61, 2.25)
Participants' education					
Not attended school	53(61.6)	33(38.4)	Ref.		Ref.
Primary school	78(69.6)	34(30.4)	0.76(0.47, 1.23)	0.266	1.12(0.62, 2.01)
Secondary school	100 (71.4)	41(29.3)	0.67(0.42, 1.06)	0.086	0.94(0.52, 1.72)
Diploma and above	79(79.8)	20(20.2)	0.43(0.24, 0.75)	0.003	0.84(0.38, 1.87)
Partner's education					
Not attended school	14(56.0)	11(44.0)	Ref.		Not included[c]
Primary school	40(67.8)	19(32.2)	0.64(0.30, 1.36)	0.247	
Secondary school	63(75.9)	20(24.1)	0.46(0.22, 0.97)	0.043	
Diploma and above	74(83.2)	15(16.8)	0.29(0.13, 0.63)	0.002	
Marital status					
Married	189(74.4)	65(25.6)	Ref.		Ref.
Single, widowed or divorced	120(65.6)	63(34.4)	1.43(1.01, 2.03)	0.042	1.25(0.82, 1.90)
Had outdoor job					
No	158(66.7)	79(33.3)	Ref.		Ref.
Yes	151(75.5)	49(24.5)	0.70(0.49, 1.01)	0.058	1.01(0.62, 1.63)
Family monthly income					
<61.0 US$	89(68.5)	41(31.5)	1.57(0.94, 2.62)	0.082	0.74(0.39, 1.40)
61.0-194.0 US$	135(67.8)	64(32.2)	1.68(1.04, 2.71)	0.032	1.44(0.84, 2.49)
>194.0 US$	85(78.7)	23(21.3)	Ref.		Ref.
Practiced BSE[a]					
No	228(67.3)	111(32.7)	Ref.		Ref.
Yes	81(82.6)	17(17.4)	0.44(0.26, 0.74)	0.002	0.59(0.32, 1.06)
Traditional medicine use before confirmation					
No	140(80.0)	35(20.0)	Ref.		Ref.
Yes	169(64.5)	93(35.5)	1.89(1.28, 2.80)	0.001	0.86(0.49, 1.49)
Symptom interval					
≤3 months	103(75.7)	33(24.3)	Ref.		
>3 months	206(68.4)	95(31.6)	1.44(0.97, 2.14)	0.070	1.87(1.15, 3.03)*

Continued …

Table 14. Continued.

Variables	Status at last contact		Bivariate Cox regression		Multivariable Cox regression
	Censored (%)	Death (%)	HR (95% CI)	P-value	HR (95% CI)
Histologic tumor grade					
Grade 1	43(82.7)	9(17.3)	Ref.		Ref.
Grade 2	98(77.8)	28(22.2)	1.35(0.63, 2.87)	0.429	1.24(0.53, 2.89)
Grade 3	56(66.7)	28(33.3)	2.19(1.03, 4.67)	0.041	1.59(0.70, 3.69)
Not specified	112(64.0)	63(36.0)	2.29(1.14, 4.62)	0.020	1.51(0.68, 3.36)
Advanced-stage at diagnosis					
No	131(90.3)	14(9.7)	Ref.		Ref.
Yes	155 (59.8)	104(40.2)	5.02(2.87, 8.78)	0.000	3.32(1.81, 6.10)***
Not specified	23(69.7)	10(30.3)	3.57(1.58, 8.04)	0.002	1.23(0.32, 4.71)
Hemoglobin level during diagnosis					
<12.0 g/dl	22(53.7)	19(46.3)	1.96(1.19, 3.23)	0.008	1.09(0.61, 1.95)
>12.0 g/dl	240(73.4)	87(26.6)	Ref.		Ref.
Not specified	47(68.1)	22(31.9)	1.18(0.74, 1.89)	0.477	0.52(0.26, 1.04)
Co-morbidities at diagnosis					
0	224(68.9)	101(31.0)	Ref.		Not included
≥1	85(75.9)	27(24.1)	0.81(0.51, 1.27)	0.357	
Surgery therapy					
No	21(28.0)	54(72.0)	Ref.		Ref.
Yes	284(82.3)	61(17.7)	0.16(0.11, 0.23)	0.000	0.23(0.15, 0.35)***
Delay to adjuvant chemotherapy					Not included
≤90 days	136(85.0)	24(15.0)	Ref.		
>90 days	62(84.9)	11(15.1)	0.90(0.44, 1.84)	0.783	
Radiotherapy received					Not included
No	207(74.7)	70(25.3)	Ref.		
Yes	96(70.1)	41(29.9)	1.09(0.74, 1.60)	0.653	
Hormonal therapy					
No	40(46.0)	47(54.0)	Ref.		Ref.
Yes	262(80.9)	62(19.1)	0.24(0.17, 0.36)	0.000	0.26(0.17, 0.40)***

[a]before symptom recognition; BSE: Breast self-examination; $=US dollar; HR=hazard ratio; *partner's education (n=256) is not included in the model since it decreases the power of the model; *p < 0.05, **p < 0.01, ***P < 0.001.

Discussion

This study determined the incidence of death and its determinants among women with breast cancer. The incidence rate of death was 146 deaths per 1000 person-years (95% CI [122.7, 173.8]). Three-fourth of the women with breast cancer were alive at two years of their diagnosis (75.2%, 95% CI [70.7%, 79.0%]). The risk of death was significantly higher among women who had diagnostic delay of >3 months following symptom recognition and diagnosed at an advanced-stage.

The two-year overall survival rate (75.2%) in our cohort showed improvement over time compared to the previous findings in the rural part of Ethiopia (53%) [8]. The observed improvement could be due to the higher rate of early-stage diagnosis of breast cancer in the Addis Ababa (35.7%) than the rural part of Ethiopia (15%) [8], and better access to treatment in our cohort than the rural, and advancement of breast cancer treatment such as endocrine therapy over the last five years.

Our estimate is comparable with the pooled estimate done for sub-Saharan African countries [25]. The overall one-, two-, and three-year survival estimates were 84.1%, 61.4%, and 52.3%, respectively. However, our finding is lower than the country-specific findings in sub-Saharan African countries like Morocco (71.4% survived for five years) [26] and Libya (75.8% survived for five years) [27]. As expected, our cohort's survival rate is lower than the global estimates of 1-, 3- and 5-year overall survival rates, which were 92.0%, 75%, and 73%, respectively [28].

This finding reflects that the survival rate of women with breast cancer in our country is lower than some African countries [26-27], and global estimates [28]. There could be several possible reasons for this discrepancy. The primary cause of this difference could be the stage at diagnosis of the women [9, 25, 29]; where 64.3% of the women with breast cancer in our cohort diagnosed at an advanced-stage, and it was the leading risk factor of death of women with breast cancer. The two-year overall survival rate for women diagnosed with stage IV was 26.7% while 100.0% for stage I. Thus, interventions targeted at downstaging the stage at diagnosis should be emphasized. In addition to the stage at diagnosis, the variation in women's survival rate with breast cancer across these countries could be accounted for the variation in the countries' development status [25].

After controlling the effect of stage at diagnosis, the risk of death was nearly two times (HR=1.77) higher among women diagnosed > 3 months of symptom recognition. Our finding concurs with Richards's and colleagues' report [11] that compared to patients with delays ≤ 3 months, those patients with > 3 months delay had 12% lower 5-year survival. This underscores that interventions targeting at shortening the time interval between symptom recognition and diagnosis are essential to improve women's survival with breast cancer. Educating women, their significant others, and primary health care providers about the symptoms, screening methods, and breast cancer management could improve the women's health-seeking behavior, thereby shortening the diagnosis interval. Breast cancer education to women could be given during their visit to maternal health services [30].

In addition to early diagnosis, timely initiation of appropriate treatment improves the prognosis. The risk of death was significantly lower among women who had surgical therapy, and those who took hormonal therapy. Delay in treatment initiation is significantly associated with an increased rate of death [31]. For example, Yu et al. found a 15% increased hazard of death among women who initiated adjuvant chemotherapy after four weeks of surgery [32], and Chavez-MacGregor et al. reported a 34% increased risk of death among those who started after 12 weeks of surgery [33]. We did not, however, found an association between delay to initiation of adjuvant chemotherapy and survival. This may, in part, reflect the short follow-up period and small sample size used, making our estimation unpowered to detect a statistically significant difference in these groups.

Several studies reported the effect of tumor's molecular subtype on the survival of the women with breast cancer [34-36]; aggressive tumors may lead to death in a shorter time interval than those with slow progressing tumors. In the unadjusted analysis, the risk of death was lower among women whose receptor status was determined (HR=0.21, p=0.002). Due to the limited number of women with known hormone receptors (11.2%), we could not demonstrate the adjusted effect of the receptor status: estrogen receptor, progesterone receptor, and Human Epidermal Growth Factor Receptor 2 on the survival of the cases.

Similar to earlier findings [25], no evidence of significant association between age and survival was detected. This result may be due to our countries' younger population distribution, where more than half of the women are having cancer before their fifties. The association could also be attenuated due to the non-linear relationship between age at diagnosis and death from breast cancer [37] and under-reporting age.

Lost to follow-up bias is one of the challenges in cohort study. In this study, however, we have considered it during the study's design, and we recorded multiple addresses (phone-cell number of the respondent and her relatives). As a result, we had only four lost to follow-ups. Thus, we can say the effect of lost to follow-up bias to our estimates is minimal. Like most of the studies [37-43], we have calculated the survival from the date of diagnosis. In doing so, the survival rate might be affected by the lead time bias; survival is shorter for these cases whose diagnosis is delayed, resulting in a shorter time of survival. However, we have calculated the survival from symptom recognition to the last follow-up. The overall survival rate computed from date of first symptom recognition is by far higher if computed from the first symptom recognition date..

Some limitations should be considered while interpreting our findings. Researchers recommend computing breast cancer-specific survival rates instead of overall survival because overall survival could be diluted by the non-breast cancer-specific deaths [44]. However, we could not determine breast cancer-specific survival due to a lack of data on specific causes of death; this may overestimate breast cancer-related mortality rate. Experts in the field, Oncology residents abstracted clinical data, but patients' medical charts may not document all the respondents' treatment modalities and their prognosis. To minimize this, we have triangulated the receipt of treatment from the study participants via phone interviews. Death was ascertained via phone interviews with their next of kin. Even though estimation of death affected a lesser extent, information on some of the dead women's treatment status was difficult to ascertain via the phone interview, which could affect our effect size calculation in the multivariable analysis. Lastly, our follow-up time was limited for about two years of diagnosis (median follow-up=25.1 months) because of logistic and feasibility concerns. The short follow-up could affect the estimated effect sizes.

Conclusions

Only 3 in 4 women with breast cancer in Addis Ababa survived two years following their diagnosis. The survival rate showed improvement over time compared to previous Ethiopia findings but is lower than in other sub-Saharan African countries and developed countries. Delay in diagnostic confirmation following recognition of symptom and advanced-stage at diagnosis are negatively associated with breast cancer survival. This underscores the need to increase awareness about the importance of prompt clinical evaluation and referral for

diagnostic confirmation and early detection to mitigate the disease's burden in Ethiopia and other parts of Africa.

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Anex VIII. Declaration

I, the undersigned, declare that this is my original work, has never been presented in this or any other University, and that all the resources and materials used for the dissertation, have been fully acknowledged.

Name: Alem Gebremariam Abraha

Signature: _____

Date: May 18, 2021____

Place: Addis Ababa, Ethiopia

Date of Examination: May 18, 2021

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

Name: Prof. Alemayehu Worku (PhD)

Signature: _____

Date: _____