Estimating and predicting the burden of breast cancer in Ethiopia.

Thesis

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Summary

As part of this Ph.D. project, we conducted a comprehensive systematic review of Breast Cancer Care in Africa, which revealed a concerning scarcity of available data on the topic in Ethiopia. The existing data predominantly concentrated on urban settings, resulting in an inadequate understanding of the burden of breast cancer in Ethiopia in rural settings. To address these gaps in data, we aimed to generate comprehensive evidence on the burden of breast cancer in rural Ethiopia by conducting four academic studies in this field.

The first study conducted was a community-based cross-sectional study to assess self-reported breast abnormalities in rural adult women. The study involved surveying nearly 8000 women who were educated about breast cancer (BC) and its symptoms. Those who reported abnormalities underwent clinical examination and cytological sampling by an experienced surgeons using ultrasound-guided fine needle aspiration cytology (FNAC). The study found low self-breast awareness among rural women, with 84.5% reporting they had never examined their breasts. The prevalence of self-reported breast abnormalities was 3.4%. In total, seven cases of breast cancer were identified, of which five were newly diagnosed, with a detection rate of 66 per 100,000 adult women. BC cases are expected to rise from 28,000 in 2018 to 40,000 in 2028, resulting in a prevalence rate of 92 per 100,000 adult women.

The second study was a survey conducted among a random sample of rural women who had experienced the death of female relatives. A modified standard verbal autopsy questionnaire was used to inquire about the cause of death, to determine breast cancer morbidity and mortality among a women residing in rural Ethiopia. In total, 4,942 women were interviewed who reported on about 21,396 female family members. Of them, 788 (3.7%) women died at the age above 15 years. The study found that breast cancer was among the leading causes of women's death in rural Ethiopia, accounting for 2.7% (95% CI 1.5–3.7%) of all deaths. Breast cancer occurred frequently in young reproductive age group with a long duration of illness. The majority of women (90.5%) died at home.

The third study investigated treatment outcomes of metastatic breast cancer (mBC) patients in Ethiopia, using data from the only large oncology center in Ethiopia. The study involved 573 individuals diagnosed with metastatic breast cancer. Metastasis occurred at the median age of 43.7 years, and the median survival time was 6.6 months. Factors influencing survival included negative hormone receptor status, grade 3 tumors, and visceral metastases. Endocrine therapy alone demonstrated better survival rates, and even better outcomes were observed when endocrine treatment followed chemotherapy. The survival rates of breast cancer patients are strongly associated with the stage at diagnosis. About 49.7% of metastatic breast cancer patients received no cancer-directed treatment.

The fourth study focused on the economic burden of breast cancer care and treatment. The study revealed that the total costs of breast cancer treatment increased with higher stages of the disease. Breast cancer care and treatment in Ethiopia are expensive, and the economic burden falls on the families and communities of breast cancer patients. Late presentation of breast cancer not only affects the survival of patients but also has a strong economic impact on families, communities, and the country at large.

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Referat

Im Rahmen dieser Dissertation führte ich eine umfassende systematische Analyse der Brustkrebsversorgung in Afrika durch, die einen besorgniserregenden Mangel an verfügbaren Daten zu diesem Thema in Äthiopien aufdeckte. Die vorhandenen Daten konzentrierten sich überwiegend auf städtische Gebiete, was zu einem unzureichenden Verständnis der Belastung durch Brustkrebs im ländlichen Äthiopien führte. Das Projekt strebt an diese Datenlücken schließen und umfassende Belege für die Belastung durch Brustkrebs, insbesonderen in ländlichen Gebieten, zu generieren. Hierfür wurden vier Studien durchgeführt.

Bei der ersten Studie handelt es sich um eine gemeinschaftsbasierte Querschnittsstudie zur Beurteilung selbstberichteter Brustanomalien bei erwachsenen Frauen in ländlichen Gebieten. Es wurden fast 8.000 Frauen befragt, die über Brustbewusstsein aufgeklärt wurden, und diejenigen, die Anomalien meldeten, wurden einer klinischen Untersuchung mittels ultraschallgeführter Feinnadelaspirationszytologie (FNAC) unterzogen. Die Studie identifizierte sieben Fälle von Brustkrebs, davon fünf neu diagnostizierte, mit einer Erkennungsrate von 66 pro 100.000 erwachsenen Frauen. Die Prävalenz selbstberichteter Brustanomalien betrug 3,4 %. Die Studie ergab, dass Frauen auf dem Land ein geringes Bewusstsein für die Brustkrebs haben: 84,5 % gaben an, ihre Brüste noch nie untersucht zu haben.

Die zweite Studie wurde durchgeführt, um die Brustkrebsmorbidität und -mortalität bei einer Zufallsstichprobe von Frauen im ländlichen Äthiopien zu bestimmen. Dabei wurde ein modifizierter Standardfragebogen zur verbalen Autopsie verwendet, der von Frauen ausgefüllt wurde, die den Tod einer Schwester erlebt hatten. Die Studie ergab, dass Brustkrebs eine der häufigsten Todesursachen bei Frauen im ländlichen Äthiopien war und häufig in der jungen gebärfähigen Altersgruppe mit langer Krankheitsdauer auftrat. 4942 Frauen wurden befragt und über etwa 21.396 weibliche Familienmitglieder berichtet. Davon starben 788 (3,7 %) Frauen im Alter über 15 Jahren. Brustkrebs gehört zu den häufigsten Todesursache bei Frauen und machte 2,7 % (95 %-KI 1,5–3,7 %) aller Todesfälle aus. Die Mehrheit der Frauen (90,5 %) starb zu Hause.

Die dritte Studie befasste sich mit den Behandlungsergebnissen von Patientinnen mit metastasiertem Brustkrebs (mBC) in Äthiopien. An der Studie nahmen 573 Personen teil, bei denen metastasierter Brustkrebs diagnostiziert wurde. Der durchschnittliche Beginn der Metastasierung erfolgte im Alter von 43,7 Jahren, mit einer mittleren Überlebensrate von 6,6 Monaten. Das Überleben beeinflussten Faktoren wie ein negativer Hormonrezeptorstatus, Tumore 3. Grades und viszerale Metastasen. Die alleinige endokrine Therapie zeigte bessere Überlebensraten, und noch bessere Ergebnisse wurden beobachtet, wenn die endokrine Behandlung auf die Chemotherapie folgte. Die Überlebensraten von Brustkrebspatientinnen hängen stark vom Stadium bei der Diagnose ab. Etwa 49,7 % der Patientinnen mit metastasiertem Brustkrebs erhielten keine krebsgerichtete Behandlung.

Die vierte Studie konzentrierte sich auf die wirtschaftliche Belastung durch Brustkrebspflege und -behandlung. Die Studie ergab, dass die Gesamtkosten der Brustkrebsbehandlung mit fortschreitendem Krankheitsstadium steigen. Brustkrebsbehandlung in Äthiopien ist teuer und die wirtschaftliche Belastung liegt bei den Familien und Gemeinden der Brustkrebspatientinnen. Eine späte Diagnose von Brustkrebs beeinträchtigt nicht nur die Überlebenschancen der Patientinnen, sondern hat auch starke wirtschaftliche Auswirkungen auf Familien, Gemeinden und das Land als Ganzes.

Contents

Abbreviations and Acronyms:

ASR	Age Standardized Rate
AOR	Adjusted Odds Ratio
BC	Breast Cancer
CDC	Center diseases control
COR	Crude Odds Ratio
CI	Confidence Interval
DHS	Demographic and Health Surveillance
EC	Ethiopian Calendar
EPHA	Ethiopia Public Health Association
FNAC	Fine Needle Aspiration Cytology
GLOBOCAN	Global Burden of cancer
GDP	Gross Domestic Product)
HF	Health Facilities
HDSS	Health and Demographic surveillance sites
HCP	Health care practitioner
HF	Health facility
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
mBC	metastatic Breast Cancer
NGO	Non-governmental Organization
OPD	Outpatients Department
OR	Odd Ratio
OS	Overall Survival
rmBC	Recurrent Metastatic Breast cancer
RT	Radiation Therapy
SD	Standard Deviation
VA	Verbal Autopsy
USA	United State of America
WHO	World Health Organization

1. Introduction and aims

Globally, breast cancer is the most common cancer among women and the leading cause of cancer-related deaths in 2020, with an estimated 2.3 million cases and 685,000 deaths. The age-standardized breast cancer incidence and mortality rates of breast cancer in women globally and in Africa in 2020 were 47.8/13.6 and 40.7/19.4 per 100,000 women, respectively [Sung et al., 2021]

The epidemiological feature of breast cancer in developing countries is characterized by a lower incidence but higher mortality rates [Da Costa et al., 2017; Ghoncheh et al., 2016]. Breast cancer incidence and mortality rates have been on the rise since 1990. Mortality rates in Sub-Saharan Africa have been experiencing an annual increase of 0.56%. [Lima et al., 2021; Azamjah et al., 2019]. In most high-income countries, more than 70% of breast cancer patients are diagnosed in early stages I and II. However, only 20-50% of patients in most low- and middle-income countries are diagnosed at early stages [Unger, 2014; Afaya et al., 2022]. Most breast cancer in women in low-income countries presents at an advanced clinical stage, resulting in limited and difficult therapeutic options and poor survival rates [Unger, 2014]. In Ethiopia, breast cancer is the leading cause of morbidity and mortality among women, with an estimated 16,000 new cases and 9,000 deaths in 2020, accounting for 32.9% of all new cancer cases and 28% of all cancer deaths among women [Sung et al., 2021]. Breast cancer screening programs are not in place, and more than 80% of breast cancer cases are diagnosed at advanced stages in Ethiopia. In Ethiopia, age-standardized mortality was higher than in Africa and worldwide, with a breast cancer mortality rate of 24.1 per 100,000 women [Sung et al., 2021]. Women living in rural areas often seek treatment from traditional healers before seeking help within the formal health system. Only 4.5% of breast cancer patients initially seek care in a cancer hospital, whereas 70% seek care first from a traditional healer or at a primary care site, and less than one-fourth have direct access to local and regional hospitals [Dye et al., 2010]. Early detection of breast cancer is an optimal approach to reducing premature breast cancer deaths in developing countries [Becker and Hans, 2008; Nelson et al., 2009]. Routine breast cancer screening using mammography in a country with a young population is less sensitive, unaffordable, and not feasible in a resource-limited setting like Ethiopia [Gøtzsche and Margrethe, 2011; Pace and Nancy, 2014; Li and Zhi M, 2015; Pace and Shulman, 2016]. However, clinical breast examination followed by ultrasound-guided FNAC is a simple and

effective strategy to downstage disease and reduce breast cancer mortality in resource-limited countries [Pagani et al., 2011]. Identifying women with self-reported breast abnormalities is crucial to detecting untreated cases at an early stage. The availability of data on breast awareness, self-reported breast abnormalities, and breast cancer in rural Ethiopia is crucial in developing a tailored intervention for future prevention and control of these diseases in rural settings. Predicting trends in breast cancer and abnormality is essential for planning health services to address the unmet need for breast treatment.

The magnitude of mortality and duration of suffering from illness are important to understand the disease burden in a population. However, in many low-income countries, no registration on the cause of death occurs due to a lack of medical death certificates or death registries. Verbal autopsy (VA) uses a questionnaire to assess details about signs and symptoms preceding the death and a physician's review to conclude a likely cause of death [Misganaw et al., 2012]. Moreover, understanding the clinical characteristics, treatment, and outcomes of breast cancer patients in low-resource countries like Ethiopia is crucial for informed decision-making, better allocation of resources, and the development of healthcare policies that can help improve the survival rates of BC patients [Kantelhardt et al., 2015]. Breast cancer cost estimation at different stages is crucial for healthcare professionals and policymakers. It helps develop cost-effective strategies, allocate resources optimally, detect the disease early, and reduce the economic burden. Policymakers can use this information to develop health financing policies and evaluate provider cost-effectiveness [Heinrich et al., 2013; Chatterjee et al., 2013].

Below is a summary of the objective of each study, along with the respective research questions addressed.

This study aimed to estimate and predict the burden of breast cancer in Ethiopia, particularly in rural settings. It explored various aspects such as breast cancer awareness, causes of death, duration of illness, characteristics, and survival rate of metastatic breast cancer patients including the economic burden of breast cancer treatment, clinical examination, and diagnosis.

The research questions that were addressed are as follows:

1. What is the prevalence of self-reported breast abnormalities and breast cancer among adult women in rural Ethiopia?
2. What are the most common underlying diagnoses of self-reported breast abnormalities among adult women in rural Ethiopia?

3. What is the significance of clinical breast examination in the early detection of breast abnormalities among women in rural Ethiopia?
4. How important is ultrasound-guided fine needle aspiration cytology (FNAC) in diagnosing breast abnormalities and malignancies among women in rural Ethiopia?
5. What is the burden of breast cancer as a cause of death among women in rural Ethiopia?
6. What are the common symptoms and duration of illness experienced by women who die from breast cancer in rural Ethiopia?
7. What are the survival rates for women with metastatic breast cancer (mBC) in Ethiopia?
8. How do the survival rates of women with mBC differ based on the stage at diagnosis?
9. What is the cost of breast cancer treatment for different stages (I, II, III, IV)?
10. How do the treatment costs for breast cancer vary based on different treatment modalities (e.g., surgery, chemotherapy, radiation therapy)?

The findings were compared globally and regionally, highlighting the importance of early detection, prevention, and better care strategies. The study also considers the recommendations of various cancer care organizations, including the National Comprehensive Cancer Network (NCCN), the World Health Organization (WHO), the International Agency for Research on Cancer (IARC) and national cancer control plans. The research emphasizes the impact of breast cancer in rural Ethiopia and underscores the need for breast awareness, economic planning, and effective prevention and care strategies. This dissertation is centered on four publications, which are listed below.

2. Discussion

This section primarily focuses on discussing the major findings of the study's dissertation, which explores the burden of breast cancer in Ethiopia. The objective here is to establish a connection between the key findings and the current national breast cancer burden and the approach to breast cancer early diagnosis and care in Ethiopia. Furthermore, the section provides a comprehensive analysis of the strengths and limitations of the dissertation, aiming to identify research gaps that should be addressed in future research. As part of this Ph.D. project, we conducted a systematic review on Breast Cancer Care in Africa, which revealed limited data in Ethiopia; even available data was predominantly concentrated on urban settings and a scarcity of data in rural settings [Kantelhardt et al., 2015]. Based on the review findings, this Ph.D. project was to generate evidence on the burden of breast cancer in Ethiopia, focusing on rural settings. The chapter discusses and concludes with essential remarks and recommendations to enhance breast cancer control in Ethiopia, specifically focusing on rural settings. To achieve a coherent flow, the discussion will begin by examining the studies on Breast Awareness, the burden of self-reported breast abnormalities, and Breast cancer morbidity and mortality in Ethiopia. This study is the main part of this Ph.D. work. Subsequent studies examining the characteristics and follow-up of metastatic breast cancer in Ethiopia and the burden of the health system cost of breast cancer treatment. These studies aimed to understand the burden of breast cancer in Ethiopia and the approach to early detection and care. The discussion will draw relevant comparisons with similar studies conducted in other settings.

Developing contextualized strategies for preventing and controlling breast cancer requires understanding breast awareness, abnormalities, and the burden of breast cancer across different geographic settings. The Ministry of Health in Ethiopia has developed the country's first cancer control plan based on the global cancer control strategy of the World Health Organization [FMOH, 2016]. The strategy aims to reduce breast cancer mortality by promoting breast self-awareness and training health workers to perform clinical breast examinations to detect breast cancer at an early stage. Clinical breast examination followed by ultrasound-guided FNAC is a simple and effective strategy to decrease breast cancer mortality in resource-limited countries [Miller and Cornelia, 2011]. Studies have documented that the system is efficient without serious complications or adverse effects for the patients [Pagani et al, 2011; Ly et al., 2016; Layfield et

al., 1993; Anderson et al., 2006]. The study from Tanzania showed that using ultrasound guidance for FNAC resulted in higher diagnostic accuracy for breast malignancies compared to conventional FNAC [Kamushaga et al., 2021].

We conducted a survey of 8000 rural women in Ethiopia, as 86% of the population in Ethiopia live in rural settings. The survey revealed that self-breast awareness was low among the women. Specifically, 84.5% of the participants reported that they had never examined their breasts, and 96.6% stated that they did not have any breast abnormality. However, this study provided us with a unique opportunity to educate over 8000 women about breast awareness. We further evaluated 246 women with self-reported abnormalities and confirmed 49 breast masses by a physical examination that met the FNAC criteria. The prevalence of self-reported breast abnormalities was 3.4% among nearly 8000 women. The proportion of women with reported breast abnormalities in the normal population was similar to studies conducted in other African countries [Ströbele et al., 2018; Ntirenganya et al., 2014] but lower than in Malawi, where trained breast health workers examined abnormalities, possibly leading to higher detection rates [Gutnik et al., 2016]. The difference in the effectiveness of identifying breast abnormalities between the two methods used in the study could be attributed to the fact that the researchers employed trained breast health workers to examine breast abnormalities, which likely increased the chances of identifying abnormalities compared to relying on self-reports of breast abnormalities.

Of the women who had a confirmed palpable breast mass and underwent ultrasound-guided FNAC by a surgeon, most were found to have benign breast disease. However, there were seven cases of breast cancer identified, out of which five were new diagnoses, with a detection rate of 66 per 100,000, which is higher than the rate estimated by IARC. Those with confirmed cases of BC had late-stage disease. In five cases, these women with BC were not aware of their disease. The average duration of illness for women with BC was 6 ± 1.5 years. Despite many women sufferings from breast morbidity in Ethiopia, the study found low rates of seeking medical care for breast abnormalities. This lack of medical attention is consistent with findings from other developing countries, attributed to the low severity of symptoms, financial constraints, and limited awareness and access to medical care [Ayele et al., 2022; Shulman et al., 2010]. Had these women not participated in our survey, it is quite possible they could have remained

untreated for their disease and ultimately died in their homes without knowledge of the cause of death.

Through this survey, we could interview seven rural women diagnosed with BC, discuss their perceptions of the disease, and follow their clinical course. Three women received tamoxifen treatment, and two women had declined oncologic care and died nine months after their diagnosis. The primary reasons were related to their negative perception of the outcome, fear of mastectomy, and no knowledge of any BC survivors. All seven women perceived being diagnosed with BC as a death sentence. It was observed that the late presentation of BC with unfavorable outcomes contributed to the negative perception of BC, leading to fatalistic attitudes towards the disease. It is essential to raise awareness about the significance of early detection of BC in improving outcomes and addressing the vicious cycle of late presentation, short survival, and fatalistic attitude of the disease to encourage women to seek medical care and improve their chances of survival.

The study revealed a higher proportion of reported breast abnormalities among young women, with considerable numbers perceiving breast abnormalities as life threatening and fearing the loss of their breasts if they seek medical care. These psychological and social impacts were particularly pronounced in young Ethiopian women, necessitating early diagnosis and awareness creation to reduce the effects.

The study shows that the estimated number of self-reported breast abnormalities and breast cancer cases in Ethiopian women is expected to increase from 2018 to 2028 due to population growth and ageing. Specifically, self-reported breast abnormalities could rise from 1.0-1.1 million in 2018 to 1.3-1.5 million in 2028. Breast cancer cases are projected to increase from 28,000in 2018 to 40,000 in 2028, resulting in a prevalence rate of 92 per 100,000 adult women. The study further reveals that breast cancer cases are expected to rise more rapidly among women aged 50 years and above. The number of patients in this age group is estimated to increase from 21,000 in 2018 to 30,0000 in 2028, resulting in a prevalence rate of 366 per 100,000 adult women. Over the next ten years, the incidence of breast cancer is projected to increase by 33.8%, with the highest increase observed among women aged 50 years and above due to population aging. These findings are important because they highlight the need for increased awareness and screening programs for breast cancer. Women should be aware of breast cancer's potential risks and symptoms and undergo regular screenings to detect the disease early

when it is most treatable. It is also crucial for healthcare providers and policymakers to consider these projections in their planning and resource allocation to ensure that adequate diagnostic and treatment services are available for women in need. The study also showed that breast cancer is becoming a growing concern in Ethiopia, and the healthcare system needs to prioritize breast examination, care, and treatment. Physical examinations and ultrasound-guided FNAC are affordable and effective methods to assess palpable breast masses and detect breast cancer at an early stage [Yu et al., 2012]. These approaches benefit countries with limited mammography-based screening programs and where most women are under 50 years old, as mammography is not recommended for this age group [UNDP, 2018]. Education initiatives should be developed to enhance referral mechanisms and access to adequate breast diagnostic and treatment facilities in rural areas to increase breast awareness among rural women. Tailored interventions involving breast cancer survivors should be developed to track the disease early and counteract negative perceptions toward treatment outcomes. Clinical breast examination followed by ultrasound-guided FNAC is a simple and effective strategy to downstage the disease and reduce breast cancer mortality in resource-limited countries. The healthcare system must swiftly expand oncology care and address common reasons people refuse oncologic care, such as negative perceptions about treatment outcomes and fear of mastectomy.

This study used a modified verbal autopsy questionnaire and a direct sisterhood approach to analyze breast cancer morbidity and mortality in rural Ethiopia. Significant rates were found, highlighting the need for targeted interventions to improve breast cancer awareness, diagnosis, and treatment in rural resource settings. Our findings showed that the median age of adult females in rural Ethiopia who died from breast cancer in this cohort was only 37 years, which is younger than the average lifespan of Ethiopian women (at the time of the survey, about 61.1 years [CSA, 2013]. Studies show high rates of young women diagnosed with breast cancer in Ethiopia, often with a late presentation [Hadgu et al., 2018; Kantelhardt et al., 2014]. It is often diagnosed late due to low breast awareness and traditional healing practices, leading to premature death. These factors negatively affect the prognosis of breast cancer in rural Ethiopia [Fregene and Lisa, 2005; Edge et al., 2014].

This study revealed that many women who died of breast cancer were of reproductive age. The high breast cancer death among women of reproductive age poses a risk to Ethiopia's recent

achievements in reducing maternal mortality. Although maternal-child health and communicable diseases have received significant attention in Ethiopia over the last two decades, less attention is given to preventing and controlling breast cancer and given low breast awareness and high-unmet need for breast care in rural settings [Ayele et al., 2021]. This also indicates the need for integrating breast care with maternal health services and attention to preventing and controlling breast cancer among women of this age group, who are often responsible for caring for their families [Galukande et al., 2021].

In our study, breast cancer was among the leading causes of death from neoplasms in women and among the top five causes of death from NCD. [Misganaw et al., 2014]. This indicates that Breast cancer is a significant public health problem in urban and rural settings in developing countries.

This study found that, in the rural setting of Ethiopia, NCDs accounted for 42.1% (95% CI 38.7–45.6%) of deaths among women, while infectious and parasitic causes accounted for 32% (95% CI 28.7–35.2%) of deaths. These findings are consistent with previous studies that have shown that women in sub-Saharan countries, including Ethiopia, suffer from a double burden of both non-communicable and infectious diseases [Ashenafi et al., 2017; Byass et al., 2014]. Effective healthcare interventions are urgently needed to improve women's health outcomes.

This study found that 90.5% of women with breast cancer died at home. Women might die without knowing the underlying cause of illness and seeking proper medical care. This is a significantly higher proportion than reported in a study conducted in Addis Ababa, the capital of Ethiopia, which reported that 71.3% of breast cancer patients died at home [Reniers and Rebbeca, 2009]. The higher proportion of deaths in the rural region might attributed to the underdeveloped infrastructure, limited health facilities, and low utilization and coverage of health services. In the rural area of Ethiopia, systemic treatment for breast cancer was unavailable, and financial constraints made traveling to Addis Ababa for treatment impossible for most women.

In this study, most women who died of breast cancer had exhibited symptoms of their illness for over a year before their death. On the other hand, infectious diseases such as malaria, acute respiratory infection, diarrhea, meningitis, and encephalitis, which accounted for 18% of all deaths in the population, had a median duration of suffering of 7 days or less. The prolonged period of illness can affect the psychosocial and economic status of households and communities in several ways. This may include disrupted family activities and productivity, anxiety or depression, the interruption of social networks of support, high out-of-pocket costs for healthcare, and reduction

in family savings and investments [WHO, 2011; Golics et al., 2013]. These intertwined, compounding economic effects can also be felt throughout families and communities. [Biney et al., 2020].

This study analyzed characteristics, survival rates, and treatment outcomes of breast cancer patients using data from Black Lion Hospital, the only oncologic therapy for BC patients in Ethiopia. The study revealed that tumor characteristics - such as histological type and grading - were similar to those in Western and other African studies, including Ethiopia [Marshall et al., 2017; Piggott et al., 2017; Kantelhardt et al., 2015; Kantelhardt et al., 2014; Kohler et al., 2015; Rambau et al., 2011]. The study found that visceral metastasis was the most common, followed by bone metastasis, similar to data from Nigeria [Adisa et al., 2011] but differs from Western settings [Marshall et al., 2017]. The study revealed that most metastatic breast cancer cases (60%) were found in urban residents, who account for less than 20% of the population. This implies that breast cancer patients living in rural areas face challenges due to a lack of access to standard medical treatment, high travel and accommodation costs, low health-seeking behaviors, and dependence on traditional healers [Sakafu et al., 2022; Osei et al., 2021; Wuur et al., 2021]. These obstacles worsen the issue and pose a serious public health concern for breast cancer patients in rural settings, given the high breast cancer burden in rural settings [Ayele et al., 2021].

In our study, the average age for diagnosis with metastatic breast cancer was 42-44 years, considered young; in the first two-thirds of Ethiopian women's life expectancy was 67 years. This is similar to other studies in Sub-Saharan Africa that have reported breast cancer at young age [Ayele et al., 2022; Adisa et al., 2011]. This age of breast cancer diagnosis contrasts with developed countries, where breast cancer is mainly diagnosed in the last third of life. [Bidoli et al., 2019.].

Our study found that women with metastatic breast cancer had a median survival time of 11.7 months. This is lower than Nigeria's median survival time of 17.5 months [Adisa, et al., 2011], and European studies have reported a better survival time of 2 years as the median survival time [Sundquist et al., 2017].

However, in our study, many patients received chemotherapy and endocrine treatment, with platinum being the preferred agent in triple-negative breast cancer. Our study found that patients with metastatic breast cancer (mBC) were rarely prescribed essential medications listed by the World Health Organization (WHO), such as aromatase inhibitors, bone-targeting agents, and

immunotherapy, including trastuzumab. Moreover, a significantly high proportion of breast cancer patients (50%) did not receive any treatment, even though endocrine treatment was available free of charge. This could be attributed to the high transport cost, which remains a significant obstacle for patients who want treatment and access to advanced oncologic therapy, particularly in developing settings with competing health priorities.

Patients with distant metastasis at the initial diagnosis had a better prognosis than those with metastasis detected during follow-up. The study highlights the need for increased awareness campaigns to promote early detection, access to modern therapy, and the importance of palliative care services for breast cancer patients in Ethiopia. Economic difficulties, long waiting times for chemotherapy, and limited access to care were identified as potential factors contributing to low survival rates. Improving access to quality treatment and palliative care is crucial to enhancing survival rates and the overall well-being of breast cancer patients in Ethiopia.

Our other study on the health system cost of breast cancer treatment found varying costs for optimal treatment of breast cancer patients. Chemotherapy was the most expensive, followed by radiotherapy and consultation costs [Demeke et al., 2022]. This study also revealed that the total costs of breast cancer treatment increased with higher stages of the disease; stages three and four cost the most at 68%, followed by stage two at 26%, and stage one at 6%. The cost of treating breast cancer poses an enormous economic burden on healthcare services. Healthcare providers must minimize the economic burden by considering the cost of inputs and infrastructure when providing breast cancer treatment.

The vicious cycle of late presentation, short survival, and fatalistic attitude of the next patients must be addressed by Involving long-term survivors could be an option. Breast examination, care, and treatment need to be argent agenda to respond to the increasing burden of breast cancer in Ethiopia. Ethiopia's health system should develop tailored interventions to track breast cancer at an early stage. The system has to be designed to involve breast cancer survivors to reduce negative perceptions towards breast cancer treatment outcomes and improve breast awareness.

2.1. Strengths and Limitations

This study has several strengths. Firstly, it used a large population-based approach by including a large sample size from different geographical settings, reflecting Ethiopia's population. Secondly, the study on self-reported breast abnormalities was verified using the double diagnostics method,

which includes clinical examination and Ultrasound-led FNAB cytological analysis done by experienced surgeons and pathologists. Thirdly, the study on breast cancer cause of death and duration of illness was the first to conduct non-demographic surveillance using the WHO 2012 verbal autopsy questionnaire. The physicians' review result showed consistency in more than two-thirds of the VA code diagnoses with intra-reviewer reliabilities of about 72% and 80%, [Misganaw et al., 2012].

Finally, the study on metastatic breast cancer in Ethiopia and Sub-Saharan Africa is the first and largest of its kind. The report provided valuable insights into the diagnosis, treatment, and outcome of patients with mBC in the region. The findings highlight the challenges faced by mBC patients in the region, particularly with regard to accessing radiotherapy.

Relying only on the women's self-reports may have missed the study's main limitation on breast abnormalities. The projection was performed assuming the expected number of breast abnormalities and breast cancers will continue to increase over time due to population dynamics and aging. However, inaccuracy of population growth, change in risk factors, and introduction of new interventions may affect the certainty of our projected results.

The study of breast cancer causes death and duration of illness study had limitations as well, as sisters were asked about a wide range of signs and symptoms that led to death in the last ten years, which might have introduced recall bias. We had 13.6% of cases with an unknown cause of death, which could have had important implications on the specific cause of death if the exact cause had not been correctly assigned. Reliability and repeatability in interpreting VAs and assigning causes of death could be limitations, but this methodology has been used in various other studies [Byass et al., 2012]. The duration of illness was determined based on information obtained from a caregiver, which might not indicate the actual duration of suffering by the patient.

The study on characteristics and survival of metastatic breast cancer, the lack of actual mortality data, and the use of discontinuation of care as a surrogate marker are limitations of the study. It is difficult to distinguish between patients who discontinued follow-up visits due to death or other reasons.

2.2. Conclusions

The study sheds light on the burden of breast cancer among women in Ethiopia. It reveals that breast cancer is a major cause of morbidity and death, especially among women in rural areas of reproductive age. The study emphasizes the urgent need to address the growing issue of breast health in the country. This can be achieved by improving access to diagnostic and treatment facilities, raising awareness about breast cancer, and developing targeted interventions to address the problem effectively and meet the high-unmet need for breast health issues. The Ministry of Health should scale up preventive and curative interventions in rural areas and introduce palliative care for cancer patients. The government, non-governmental organizations, and healthcare providers should collaborate to develop and implement adequate breast cancer services within the primary healthcare system. The study reports a relatively high number of late-stage cancer patients, resulting in a long duration of illness and reduced survival rates. Late detection of breast cancer incurs high costs in terms of treatment, morbidity, and mortality. Therefore, it is crucial to raise awareness campaigns to reduce the proportion of these patients and shift patients towards curable diseases. Improving access to modern therapy and palliative care services would help increase the survival rate of breast cancer patients. Holistic care is essential, especially considering the young age of these patients, who are often the primary caregivers for their families.

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4. Thesis

1. The prevalence of self-reported breast abnormalities was 3.4% among the study population. Of those, 15.7% had ever been examined, and 41.8% sought treatment. Out of 49 cases, 44 were benign breast disease and 5 were newly diagnosed as breast cancer, resulting in a detection rate of 66 per 100,000 (95% CI, 8–123 per 100,000).
2. The mean duration of illness for women with BC was 6 ± 1.5 years, whereas the mean time of illness was 2.7 ± 0.7 years for women with benign breast diseases ($p = 0.001$).
3. We predict, based on population changes alone, that the future demand for breast diagnosis in the next ten years will be 1.5 million for women with self-reported breast abnormalities; of these, 282,000 women with breast abnormalities may meet the criteria for FNAC. The projected BC numbers will increase from an estimated 28,000 (95% CI, 5,000–51,000) in 2018 to 40,000 (95% CI, 7,000–72,000) in 2028, with a prevalence rate of 92 per 100,000 adult women. The average percentage increase in the number of BC cases between 2018 and 2028 is 32.6%– 33.8%. The prevalence rate for breast cancer among women aged 35-49 is expected to be 90 per 100,000 adult women, while for women aged 50 or older, the prevalence rate is expected to be 400 per 100,000 adult women.
4. The median age of breast cancer deaths was 37 years (IQR 26–45), which is substantially lower compared to the median age for deaths from other diseases, with a median of 46 years (IQR 32–60).
5. A majority of breast cancer deaths (52.3%) occur in women aged 15-49, while 38.1% occur in women aged 50-64.
6. Breast cancer accounts for 2.7% (95% CI 1.5–3.7%) of deaths, making it the second leading cause of death from neoplasms and one of the top five causes of death from NCDs among women.
7. The average duration of illness for women who died of breast cancer was about 365 days. In contrast, infectious diseases like malaria, acute respiratory infection, diarrhea, meningitis, and encephalitis, which accounted for 18% of all deaths in the population, had a shorter median duration of suffering of 7 days or less. About 90.5% of women died at home in rural Ethiopia

8. The average age at the time of first metastasis was 43.7 $\pm$ 11.9 years, with an average survival probability of twelve months.
9. The estimated mean OS with metastasis was 11.7 months (range from 0 to 138 months, median 6.6 months). High grading (HR=1.85 [95% CI 1.24- 2.77] p=0.003), negative hormone receptor status (HR=1.72 [95% CI 1.17-2.54] p=0.006), and visceral metastasis (HR=1.56 [95% CI1.18-2.08] p=0.002) indicated a more favorable survival as significant and independent prognostic factors. Endocrine treatment (only: HR=0.52 [95% CI 0.35-0.77] p=0.001); sequential to chemotherapy: HR=0.34 [95% CI 0.23-0.49] p<0.001) were associated with better overall survival.
10. Breast cancer treatment cost was the highest for patients in stages three and four, at 68%, followed by stage two at 26% and stage one at 6%.

Synopsis of the Publications

Publication one:

Wondimu Ayele, [1,2] Adamu Addissie, [1] Andreas Wienke, [2] Susanne Unverzagt, [2] Ahmedin Jemal, [4] Lesley Taylor, [5] and Eva J. Kantelhardt[2,3]; Breast Awareness, Self-Reported Abnormalities, And Breast Cancer In Rural Ethiopia: A Survey Of 7,573 Women And Predictions Of The National Burden." *The Oncologist* Vol. 26,6 (2021): E1009-E1017. Doi:10.1002/Onco.13737.

Author's contribution

I played a significant role in this project. I was responsible for generating ideas, formulating research questions, designing the study, and conducting fieldwork under the guidance of my supervisor. I managed the entire field mission, including recruiting data collectors and supervisors, supervising data collection, and overseeing follow-up care for women as per the study protocol. I ensured data quality control, analyzed the results, and wrote the manuscript. Additionally, I took all the necessary steps until the paper was published.

Publication two:

Wondimu Ayele,[1,2] Amand Führer,[2] Gabriele Anna Braun,[2] Franziska Formazin,[2] Andreas Wienke,[2] Lesley Taylor,[3] Susanne Unverzagt,[4] Adamu Addissie,[1,2] and Eva J. Kantelhardt[2]

: Breast cancer morbidity and mortality in rural Ethiopia: data from 788 verbal autopsies." *BMC Women's Health* vol. 22,1 89., doi:10.1186/s12905-022-01672-7

Author's contribution I was the main person responsible for the conception of ideas, formulation of research questions, design, and conducting the actual fieldwork, extracting data with support from the main supervisor. I was also responsible for quality assurance, analysis of the data, writing of the results, and development of the manuscript with support from my supervisors. I was also responsible for all the required actions until the paper was published.

format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

Publication three:

Bibliographic Information

Christina Mirjam Weiner [1], Assefa Mathewos [2], Adamu Addissie [3], Wondimu Ayele [3], Abraha Aynalem [2], Tigeneh Wondemagegnehu [2], Andreas Wienke [4], Ahmedin Jemal [5], Peter Zerche [6], Christoph Thomssen [7], Andreas Seidler [8], Eva Johanna Kantelhardt [9]: Characteristics and follow-up of metastatic breast cancer in Ethiopia: a cohort study of 573 women.
The Breast (2018), doi: 10.1016/j.breast.2018.08.095

Author's contribution: I actively participated in refining methodology, writing results, and discussion and conclusion, along with other authors. I also revised the manuscript and approved it for publication.

Publication four:

Tamiru Demeke [1 2], Wondimu Ayele [1 2], Damen Haile Mariam [2], Andreas Wienke [1], Mathewos Assefa [3], Adamu Addissie [1 2], Rafael Mikolajczyk [1], Susanne Unverzagt [4], Eva Johanna Kantelhardt [1 5]: Health system cost of breast cancer treatment in Addis Ababa, Ethiopia." PloS one vol. 17,10 e0275171., doi: 10.1371/journal.pone.0275171.

Author's contribution: I played a key role in conceptualizing the project, designing the methodology, conducting the analysis, ensuring quality assurance, producing tables and graphs, writing the report and manuscript, and overseeing the entire publication process. Specifically, my contributions included conceptualization, formal analysis, methodology, and writing in reviewing and editing.

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Global Health and Cancer

Breast Awareness, Self-Reported Abnormalities, and Breast Cancer in Rural Ethiopia: A Survey of 7,573 Women and Predictions of the National Burden

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Breast neoplasms • Health services • Ethiopia

Abstract

Background. Breast cancer (BC) is the most frequently diagnosed cancer and leading cause of cancer deaths among women in low-income countries. Ethiopia does not have a national BC screening program, and over 80% of patients are diagnosed with advanced stage disease. The aim of this study was to assess how many women self-report a breast abnormality and to determine their diagnoses in rural Ethiopia.

Methods. A community-based cross-sectional study was conducted among 7,573 adult women. Women were interviewed and educated about breast awareness, and those who reported breast abnormalities underwent clinical examination by experienced surgeons. Ultrasound-guided fine needle aspiration cytology (FNAC) was obtained, and cytological analysis was performed. The findings were projected to the female population of Ethiopia to estimate current and future burden of diseases.

Findings. Of the 7,573 women surveyed, 258 (3.4%) reported a breast abnormality, 246 (3.2%) received a physical examination, and 49 (0.6%) were found to be eligible for ultrasound-guided FNAC or nipple discharge evaluation. Of all the cases, five (10.2%) breast malignancies were diagnosed. We projected for Ethiopia that, approximately, 1 million women could self-report a breast abnormality, 200,000 women could have a palpable breast mass, and 28,000 women could have BC in the country.

Conclusion. The health care system needs to build capacity to assess and diagnose breast diseases in rural areas of Ethiopia. These data can be used for resource allocation to meet immediate health care needs and to promote detecting and treating BC at earlier stages of disease. ***The Oncologist*** 2021;26:e1009–e1017

Implications for Practice: Routine mammography screening in a resource-limited country with a young population is neither sensitive nor affordable. Clinical breast examination with consecutive ultrasound-guided fine needle aspiration cytology may ensure early diagnosis, downstage disease, and reduce breast cancer mortality. This study had the unique opportunity to educate over 7,573 rural women about breast abnormalities and offer clinical and cytological diagnosis for reported breast abnormalities. The findings were extrapolated to show the nationwide burden of breast abnormalities and unmet diagnostic needs. These data will serve as policy guide to improve adequate referral mechanisms and breast diagnostic and treatment facilities.

Introduction

In Ethiopia, breast cancer (BC) is the most frequently diagnosed and most prevalent cancer in women, as well as the second leading cause of cancer death. The recent publication of GLOBOCAN estimates an annual number of 15,244

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new cases and 8,159 deaths. A reported 25,156 women have been diagnosed with BC over the last 5 years [1–3]. This number is comparable to the estimated number of pregnancy-related deaths in the country, but BC care remains underfunded and underdeveloped. For a country of 107 million people, one centralized comprehensive cancer center with one radiation machine exists in the capital city of Addis Ababa. Patients with BC suffer from poor survival and are often diagnosed at a young age [4–5]. BC screening programs are not in place, and more than 80% of BCs are diagnosed at an advanced stage. Early detection of BC is an optimal approach to reduce premature BC deaths in developing countries [6–7]. Routine BC screening using mammography in a country with a young population is less sensitive, unaffordable, and not feasible in a resource-limited setting like Ethiopia [8–11]. Clinical breast examination followed by ultrasound-guided fine needle aspiration cytology (FNAC) is a simple and effective strategy to downstage disease and reduce BC mortality in resource-limited countries [12]. Studies have documented that the strategy is efficient without serious complications or adverse effects for the patients [13–17]. Clinical breast examination is recommended by guidelines [18] and was recently introduced in Ethiopia. To reach the general population, examination by lay volunteers has been shown to be effective but involves high costs [19]. This study aimed to assess and offer a diagnostic workup for women with self-reported breast abnormalities to investigate the magnitude of rural women who would use diagnostic services if public awareness and diagnostic health services were in place.

In the absence of up-to-date data on the magnitude of BC abnormalities and cancer in rural Ethiopia, developing tailored interventions for the future prevention and control of the disease are major challenges [20]. Identifying women with self-reported breast abnormalities provides the opportunity to detect untreated BC cases at early stages. The aim of this study was to estimate the proportion of adult women with self-reported breast abnormalities in a rural region of Ethiopia, assess the diagnosis of these abnormalities, and extrapolate the disease burden for the entire Ethiopian female population.

Materials and Methods

Study Design and Population

This community-based cross-sectional study was conducted at the Butajira Health and Demographic Surveillance Site (HDSS) in Ethiopia. The site is located in a densely populated area within a rural region in the South. The HDSS was created in 1986 to continuously collect longitudinal population health and health-related data and to provide infrastructure for additional studies. Currently, over 78,000 inhabitants are under surveillance in this site. The people reside in nine rural and one urban "kebeles" (neighborhoods) [21]. The kebeles are further classified based on geographic zones as highland, midland, and lowland areas. The area is considered a representative cross-section of Ethiopia's diverse population and living conditions, as over 73% of Ethiopia's female population lives in rural areas. Patients typically receive care in health posts or in health centers and then receive a more complex diagnostic workup and treatment for medical conditions in hospitals. In the context of BC, patients receive physical examination by surgeons, fine needle aspirations, surgeries, and endocrine therapies in the zonal hospital. Patients requiring chemotherapy or radiation would be sent to the regional hospital or to the national comprehensive cancer center, Black Lion Hospital, Addis Ababa, which at the time of this study has the country's only radiation machine. The data for this study were collected from March 2018 to April 2018.

Sampling Size and Sampling Procedure

The sample size of 7,580 women was calculated using the single proportional sample size determination formula. In similar settings of rural patients in sub-Saharan Africa, the reported proportion of women with a self-detected breast abnormality had been found to be 3.5% [22]. We assumed 10% variation in our setting, assuming 95% confidence intervals (CIs) and 0.8% margin of error. We used a design effect of 2 for intra-kebele correlation and 10% upward adjustment for nonresponses. A two-stage stratified cluster sampling technique was used. The demographic information of nine kebeles were reviewed for number of houses and number of female residents. Three kebeles were located in the highland area, three in the midland area, and three in the lowland area. All of the kebeles were considered rural (as defined by central statistics agency concepts and definitions) [23], except for one kebele located in a midland area.

Data Collection and Variables

Data on self-reported breast abnormalities were collected based on a structured data collection tool with options for open responses and were adapted from the National Comprehensive Cancer Network guidelines [18]. Prior to the actual survey, an assessment was conducted and revealed that women preferred face-to-face interviews by female interviewers. Female data collectors, health extension workers, and supervisors were instructed on breast self-awareness and the signs, symptoms, risk factors, and interventions for breast abnormalities, including clinical assessment by a surgeon, ultrasound-guided FNAC, and referral within the health care system when needed.

Twenty female data collectors and two supervisors collected data on sociodemographic factors, gynecologic history, breast health awareness, and whether participants sought care for medical problems within the health care system or with traditional healers. Women were asked if they had any breast abnormalities, including nipple discharge, mass, skin changes, burning sensation, nipple retraction, redness, pain, or any other condition felt to be abnormal compared with baseline. Women who reported self-detected breast abnormalities were further asked about any past history of breast problems and whether the symptoms resolved or persisted. Those with active complaints were referred to the nearby health center for a physical examination by a surgeon and consideration of ultrasound-guided FNAC. The surgeon performed ultrasound-guided FNAC for palpable breast lesions and cytologic assessment of nipple discharge. An experienced pathologist interpreted the cytology slides. Women diagnosed with suspected BC were referred for oncologic

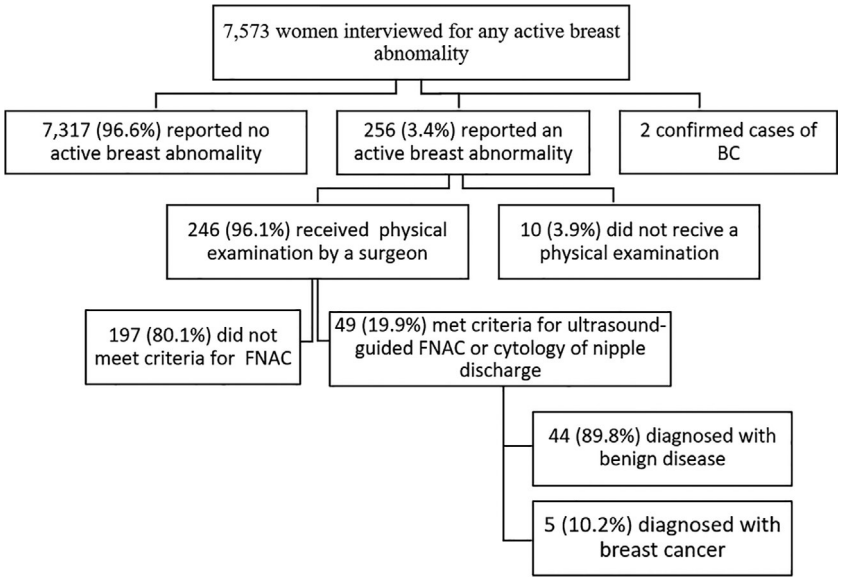

Figure 1. Diagram of self-reported breast abnormalities among study participants (five repeated FNACs). Abbreviations: BC, breast cancer; FNAC, fine needle aspiration cytology.

care at Butajira Hospital. Ethical clearance was obtained from the institutional review boards of the College of Health Science in Addis Ababa University. Written consent was obtained from each woman before starting the interview, and an informed consent was obtained from parents of participants between 15 and 18 years of age. Women with BC were linked to the nearby hospital for free oncology care.

Statistical Analysis

Data were checked for completeness and inconsistencies, entered into Epi Info version 3.5, and analyzed by statistical software SPSS version 23. Descriptive statistical methods were used to summarize sociodemographic, clinical, and pathologic characteristics and reported breast abnormalities. Projections of the burden of benign and malignant breast disease were computed as prevalence for the next 10 years. We assumed a moderate and rapid rate of Ethiopian population growth and increase in life expectancy [23–25]. Our predictions of future disease burden were based on projections from United Nations population data on the expected population growth and extrapolation within age-specific strata. Pearson chi-square and Fisher's exact tests were used to assess the factors associated with self-reported breast abnormalities (Fig. 1).

Results

Sociodemographic Characteristics

The mean ± SD age of the study participants was 35 ± 15 years. Breast abnormalities were self-reported more frequently among women between the age groups of 25–34 years and 35–49 years ($p < .001$). In our survey, 5,285 (69.8%) women lived in rural areas. We found that the majority of women, 5,066, (66.9%) were married, 3,944 (52.1%) had no formal education, 5,345 (70.6%) were Muslim, and 5,557 (73.4%) perceived themselves as having a "medium" economic status in their society (Table 1).

Breast Awareness, Symptoms of Abnormalities, and Treatment Sought

Of the total 7,573 women surveyed, 3,281 (43.3%) had heard about a breast examination, but only 1,188 (15.7%) had actually ever examined themselves. We found 256 (3.4%) women had current breast abnormalities. Women with reported breast abnormalities were asked about major symptoms: 130 (50.8%) reported pain, 91 (35.5%) reported a mass or lump and 7 (2.7%) reported nipple discharge. Respondents were asked for perceived causes of the symptoms: 169 (66.0%) mentioned sun stroke (locally known as "Mitch"), 57 (24.0 %) said "I do not know," and 14 (5.5%) thought their breast problem was cancer.

Of the 256 women who reported active breast abnormalities, 107 (41.8%) said they sought treatment before. Of these, 85 (79.4%) sought care at health facilities, 10 (9.3%) went to a traditional healer, and 12 (11.2%) visited both traditional healers and health facilities.

The 107 women then were asked about the care they received: 66 (61.7%) had received medication, such as analgesics or antibiotics; 14 (13.1%) had surgery (excisional biopsy); and 8 (7.5%) received traditional medicine (Table 2).

Reproductive Health Characteristics

Of the 256 women with current breast abnormalities, 135 (52.7%) used modern family planning methods. Of these, 16 (10.7%) took oral contraceptives. The mean age of menarche for the study participants was 15 years ± 1 year, and the age of first live childbirth was 19.6 years ± 2.7 years. The mean duration of breastfeeding was 2 years ± 0.6 years. We observed that breast abnormalities were associated with use of modern family planning methods ($p < .001$), current breastfeeding ($p < .001$), early age of menarche ($p < .001$), and older age at first birth ($p < .015$) (Table 3).

Table 1. Sociodemographic characteristics of women in Butajira Health and Demographic Surveillance Site, Southern Ethiopia, 2018

Sociodemographic variables	*n* (%)
Age group	
15–24	1,959 (25.9)
25–34	2,047 (27.0)
35–49	2,200 (29.1)
>49	1,367 (18.1)
Residence	
Urban	2,288 (30.2)
Rural	5,285 (69.8)
Marital status	
Single	1,458 (19.3)
Married	5,066 (66.9)
Divorced/separated	219 (2.9)
Widowed	830 (11.0)
Education status	
No formal education	3,944 (52.1)
Could read and write	382 (5.0)
Primary education (grade 1–8)	2,147 (28.4)
Secondary education (grade 9–12)	876 (11.6)
Tertiary education (grade >12)	223 (2.9)
Religion	
Orthodox	1,513 (20.0)
Muslim	5,345 (70.6)
Protestant	711 (9.4)
Catholic	4 (0.1)
Perceived economic status	
High	155 (2.0)
Medium	5,557 (73.4)
Low	1,861 (24.6)

Medical Comorbidities and Social and Family History

Of the 256 women with reported breast abnormalities, 19 (7.4%) indicated that they had other medical problems. We found 68 (26.6%) reported that they had chronic diseases, such as kidney diseases (24 or 9.4%), hypertension (10 or 3.9%), cardiac disease (5 or 2.0%), tuberculosis (4 or 1.6%), diabetes (1or 0.4%), and other chronic diseases (not otherwise specified; 23 or 9.0%); 43 (16.8%) women reported a history of alcohol consumption, and 108 (42.2%) chewed khat, whereas we found that only two (0.03%) were ever smokers. A total of 33 (12.9%) women with reported breast abnormalities had a family history of BC, specifically, 25 (78.2%) in a first-degree relative (mother or sister) and 7 (21.2%) in a second-degree relative (uncles or aunts).

By comparison, 2.4% of women without self-reported breast abnormalities had a family history of BC (supplemental online Table 1). We found that self-reported breast abnormalities were associated with a family history of BC ($p < .001$), positive medical history of a chronic disease ($p < .001$), and a history of having an abnormality or mass in another part of the body ($p < .004$).

Table 2. Breast self-awareness and self-reported abnormalities among 7,573 women in Butajira Health and Demographic Surveillance Site, Southern Ethiopia, 2018

Questions	*n* (%)
Have you ever heard of breast self-examination?	
Yes	3,281 (43.3)
No	4,292 (56.7)
Have you ever examined your breast for abnormalities?	
Yes	1,188 (15.7)
No	6,385 (84.3)
Do you have any breast abnormalities now?	
Yes	256 (3.4)
No	7,317 (96.6)
What kind of symptoms did you have? (*n* = 256)	
Breast pain	130 (50.8)
Nipple discharge	24 (9.4)
Breast skin changes	4 (1.6)
Mass/lump	91 (35.5)
Nipple discharge/breast skin change	7 (2.7)
What did you think is the possible cause of the symptom? (*n* = 256)	
Sun stroke (“Mitch”)	169 (66.0)
I do not know	57 (24.0)
Cancer	14 (5.5)
Wound	8 (3.1)
Breastfeeding	3 (1.2)
Other	5 (2.0)
Did you seek treatment?	
Yes	107 (41.8)
No	149 (58.2)
Where did you seek care/treatment? (*n* = 107)	
Traditional healer	10 (9.3)
Health facility	85 (79.5)
Health facilities and traditional healers	12 (11.2)
What kind of care did you receive? (*n* = 107)	
Traditional healer/regions’ place (holy water)	8 (7.5)
Medication (painkiller/antibiotics)	66 (61.7)
Surgery	14 (13.1)
Other	3 (2.8)
Traditional/medication (painkiller/antibiotics)	12 (11.2)
Nothing	4 (3.7)

Diagnosis of Patients with Self-Reported Breast Abnormalities

We interviewed 7,573 women and found that 256 (3.8%) reported current breast abnormalities and 2 reported current known BC. Of the 256 women with self-reported current breast abnormalities, 246 (96.1%) underwent physical examination by a surgeon. The clinical diagnosis was documented. The surgeon determined that 121 (49.2%) women had breast tenderness or cyclical mastalgia, 54 (27.4%) had

Table 3. Age and reproductive characteristics of study participants in Butajira Health and Demographic Surveillance Site, southern Ethiopia, 2018

Age and reproductive characteristics	Women with a breast abnormality, *n* (%)	Women without a breast abnormality, *n* (%)	*p* value
5-year age categories			
15–19	7 (2.7)	1,103 (15.1)	.015
20–24	33 (12.9)	817 (11.2)	
25–29	54 (21.1)	1,092 (14.9)	
30–34	49 (19.1)	851 (11.9)	
35–39	56 (21.9)	1,014 (13.9)	
40–44	21 (8.2)	647 (8.8)	
45–49	13 (5.1)	449 (6.1)	
50–54	12 (4.7)	403 (5.5)	
55–59	4 (1.6)	236 (3.2)	
60–64	4 (1.6)	297 (4.1)	
≤65	3 (1.2)	408 (5.6)	
Ever used modern family planning			
Yes	135 (52.7)	2,540 (34.7)	.001
No	121 (47.3)	4,777 (65.3)	
Type of family planning used			
Pills	16 (10.7)	310 (4.2)	
Implant	24 (16.1)	661 (9.0)	
Injectable/DPO	95 (62.9)	1,590 (21.7)	
IUCD	1 (0.7)	35 (0.5)	
Have you ever been pregnant?			
Yes	228 (89.1)	5,574 (76.2)	.001
No	28 (10.9)	1,743 (23.8)	
Are you currently breastfeeding?			
Yes	99 (43.9)	1,788 (32.1)	.001
No	130 (56.8)	3,781 (67.9)	
Age at menarche?			
≤11	11 (4.3)	47 (0.6)	.001
12	1 (0.4)	165 (2.3)	
13	17 (6.6)	565 (7.7)	
14	56 (21.9)	1,624 (22.2)	
≥15	171 (66.8)	4,916 (67.2)	
Age at first birth?			
<19	107 (46.9)	2,997 (54.0)	
19–24	100 (43.9)	2,249 (40.6)	.001
≥25	21 (9.2)	299 (5.4)	

Abbreviations: DPO, Depo-Provera; IUCD, intrauterine contraceptive device.

physiological changes because of pregnancy and lactation, 12 (6.1%) had bacterial infection or breast abscess, and 49 (19.9%) had a palpable breast mass or nipple discharge, which met criteria for ultrasound-guided FNAC or cytologic examination. On final pathology review of those 49 cases, the most common diagnosis was benign breast disease (Fig. 2). Five patients (10.2%) were diagnosed with BC after clinical examination and FNAC.

Clinical Presentation and Physical Examination of Women with Breast Abnormalities

We calculate the prevalence of BC to be 66 per 100,000 adult women (95% CI, 8–123 per 100,000). When including the two cases of already confirmed BC in our survey population, we calculated the prevalence of BC among rural women as 92 per 100,000 women (95% CI, 24–161 per 100,000). The mean age of women with BC was 58 ± 7.8 years. Of the women aged >49 years, nine presented with breast abnormalities, and four were diagnosed with breast cancer, whereas only 1 of 40 (81.6%) women aged <50 years was diagnosed with BC. In contrast, the mean age of women with benign breast diseases was younger, 36 ± 1.5 years. We found that BC was associated with the age group ≥49 years ($p < .002$) and with age at first birth ($p < .001$). The mean duration of illness for women with BC was 6 ± 1.5 years, whereas the mean duration of illness was 2.7 ± 0.7 years for women with benign breast diseases ($p = .001$). The average size of the mass for patients with BC was 6 cm. The mean size of the benign breast masses was 2.2 cm.

Two women interviewed had been previously diagnosed with BC. The first patient, who was aged 56 years and had received surgery, was taking adjuvant tamoxifen with regular follow-up and surveillance. The second patient was aged 78 years and had been referred to the capital city of Addis Ababa for treatment. She declined to travel to Addis Ababa because she reported a negative perception of the outcome.

Five women who participated in the survey were ultimately diagnosed with BC. The first patient, aged 80 years, presented with a locally advanced ulcerated lesion >5 cm, was referred for care within the health system, was found to have metastatic disease, and then received tamoxifen. The second patient, aged 56 years, presented with an inoperable ulcerated breast lesion greater than 5 cm. She declined all forms of treatment because of negative perceptions about the outcome and ultimately died 9 months after her diagnosis at home. The third patient, aged 48 years, presented with an ulcerating inoperable tumor measuring 4 cm, was found to have metastatic disease, and received tamoxifen. The fourth patient, aged 35 years, presented with an ulcerating tumor measuring 3 cm (grade 1), received tamoxifen, and died 6 months after her diagnosis. The fifth patient, aged 70 years, presented with an ulcerating 3 cm breast mass and declined surgery and all forms of treatment, stating, "I do not want to lose my breast."

Future Burden of BC and Breast Abnormalities in Ethiopia

We projected our findings to the general population of Ethiopian women and also accounted for anticipated population growth over the next 10 years. We found that the number of self-reported breast abnormalities could increase from 1.0–1.1 million in 2018 to 1.3–1.5 million in 2028. We project 196,868 to 210,604 breast abnormalities could have met the criteria for ultrasound-guided FNAC in 2018 in the entire country. When projected to 2028, we calculate that 241,263 to

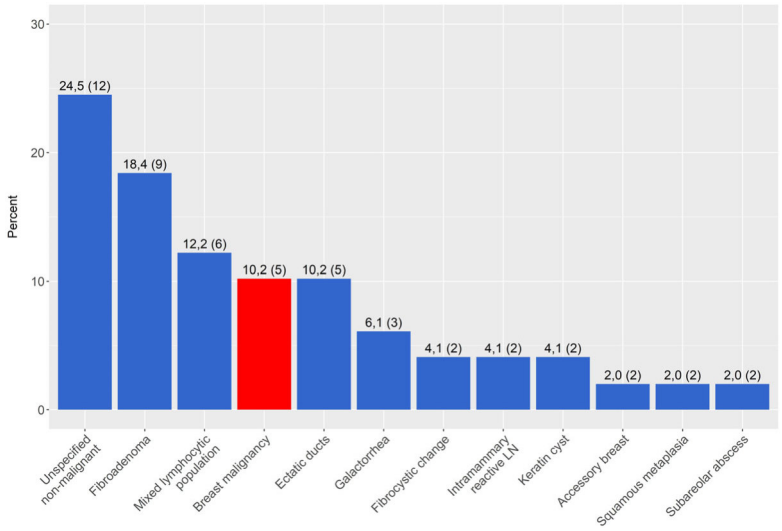

Figure 2. Fine needle aspiration cytology findings of women with a breast mass (*n* = 49).
Abbreviation: LN, lymph node.

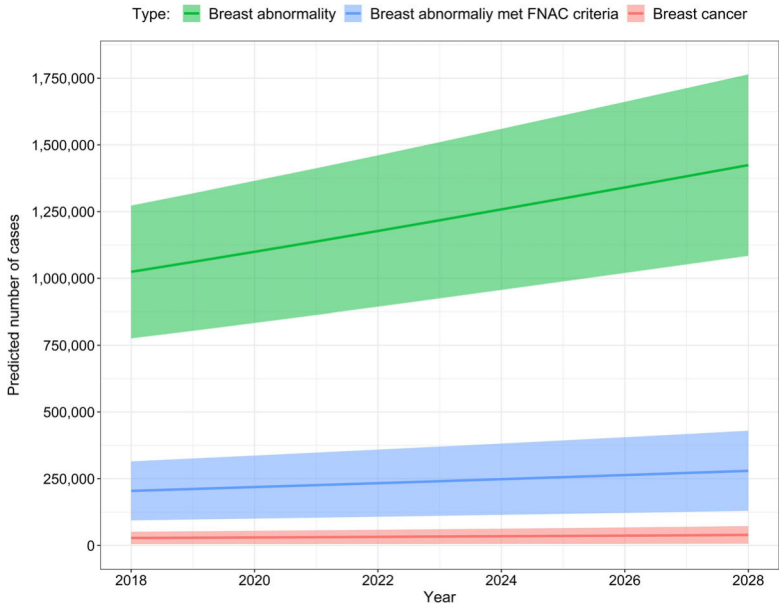

Figure 3. Projected absolute number of reported breast abnormalities (green), palpable breast abnormalities meeting criteria for fine needle aspiration cytology (blue), and cases of breast cancer (red) in Butajira 2018–2028 (projection based upon fast population growth and population pyramid 1950–2100 projection).
Abbreviation: FNAC, fine needle aspiration cytology.

281,777 women would need diagnostic services around the country, an estimated 647 per 100,000 adult women.

The projected BC numbers will increase from an estimated 27,967 (95% CI, 4,759–51,175) in 2018 to 39,552 (95% CI, 6,667–72,436) in 2028, with a prevalence rate of 92 per 100,000 adult women. The average percentage increase in absolute number of BC cases between 2018 and 2028 is 32.6%–33.8%. The annual average percentage increase is 3.3%–3.4% per year. We categorized the data in three age groups. The projected increase in BC cases among women aged 35 to 49 years will increase from 6,509 in 2018 to 9,616 in 2028, a 47.7% increase. We predict that the prevalence of BC in 2028 will be 90 per 100,000 adult women in this age bracket. For women aged ≥50 years, the number of BC cases will increase from 21,406 in 2018 to 30,112 in 2028, a 40.7% increase (Fig. 3). The prevalence for this age group will be 366 per 100,000 adult women.

Discussion

This study is, to our knowledge, the first large population-based study to assess self-reported breast abnormalities among adult women in rural Ethiopia. We observed that self-breast awareness in 7,573 rural women was low. Importantly, 84.5% of women reported they never had examined their breasts, and 96.6% of women stated that they did not have a breast abnormality. This study enabled the unique opportunity to educate over 7,573 women about breast

awareness. We were able to further evaluate 246 women with self-reported abnormalities, confirmed 49 breast masses by physical examination that met criteria for FNAC, and found seven cases of BC in the region. Three women who otherwise would not have received any attention for their BCs were linked with oncologic care services within the region. We have projected the future needs for breast care in the Ethiopian health care system, focusing on the rural population.

The magnitude of future cases of breast abnormalities, demand for diagnostic services, and need for treatment of BC cases were projected for the next 10 years based on predictions for population growth and aging in the country. The proportion of women with self-reported breast abnormalities in our normal population was 3.4%, which was similar to studies from other African countries [22, 26]. These finding were lower than a study conducted in Malawi that reported a prevalence of 7% with regard to breast abnormalities [27]. This difference could be explained by the fact that the researchers in that study used trained breast health workers to examine breast abnormalities; therefore, this method may have had a higher probability of identifying abnormalities compared with the method of self-reporting abnormalities. The major limitation of our study is that it may underestimate the actual burden of disease. We predict, based on population changes alone, that the future demand for breast diagnosis in the next 10 years will be 1.5 million for women with self-reported breast abnormalities. We project that 281,777 women with breast abnormalities may meet the criteria for FNAC, and we project that 40,254 BC cases could be identified. A limitation of this study is that we projected future disease burden by extrapolating our regional survey data to make predictions for the national burden, assuming a quickly growing and aging population. We believe that these data to a certain extent reflect the actual population because our sample survey of women in the rural region consisted of demographic characteristics, like age distribution and rural residence, that mirror the national composition of the population. We did not adjust our projections for rural/urban differences because few urban women were included in our sample. In an area without diagnostic service or breast cancer screening program, we were unable to assess the incidence of breast cancer.

We were able to survey behaviors of women when they self-detected an abnormality and found that few sought medical attention. This finding is consistent with another study that showed a high unmet need of addressing breast abnormalities in developing countries because of the low severity of symptoms, financial constraints within the health care system, low awareness about breast abnormalities among health care professionals and the public, and general lack of access to medical care [28].

We were able to provide further analysis of the underlying diagnosis in 3.4% of patients who self-detected their abnormalities, and we identified associated factors. A considerable number of young women in our study reported cyclical breast swelling, tenderness, and pain, which might be explained by hormonal changes related to lactation, pregnancy, and the menstrual cycle in a young age group.

In our study, a higher proportion of BC was diagnosed among women over the age of 49 years who complained of a breast abnormality. This finding concurred with findings from Rwanda that reported a higher proportion of BC cases among women aged $\geq$50 years with a palpable mass [29].

For those women with a confirmed palpable breast mass who underwent ultrasound-guided FNAC by a surgeon, the majority had benign breast disease. We found seven women with BC. These findings were lower than a study conducted in Kenya that reported 14 cases of BC among 1,094 adult women [30]. This difference could be explained by the fact that our study population was younger and BC was diagnosed only in women with self-reported breast abnormalities; we have not been able to detect BC among asymptomatic women. Those with confirmed cases of BC had late stage disease. In five cases, these women with BC were not aware of their disease. The low awareness about breast cancer and treatment may be due to a variety of reasons, including lack of health care seeking behavior, lack of access to BC diagnostic services, and lack of routine BC early detection programs in the country [10]. Had these women not participated in our survey, it is quite possible they could have remained untreated for their disease and ultimately died in their homes, without knowledge of the cause of death. As a result of participating in our survey, three women received tamoxifen treatment, and two declined any formal treatment.

This survey allowed us to interview seven rural women who we diagnosed with BC, discuss their perceptions of the disease, and follow their clinical course. Two women died 9 months after their diagnoses; they had declined oncologic care. The major reasons were related to their negative perception about outcome, fear of mastectomy, and no knowledge of any BC survivors. All seven women perceived being diagnosis with BC as a death sentence. We observed that the late presentation of BC with unfavorable outcome was contributing to the negative perception about BC. Raising awareness that the early detection of BC improves outcomes is needed.

The findings in our study underestimated the disease burden of breast abnormalities because clinical examination was performed only on symptomatic patients. Nevertheless, it provides a starting point to plan resource allocation in the health care system. In accordance with the National Cancer Control Plan, the Ethiopian health care system is improving access to adequate breast diagnostic and treatment facilities in rural part of the countries to respond to the unmet needs of breast abnormalities among women. The population is aging, and resource allocation for future cancer control initiatives needs to be planned. When the country increases breast awareness, it would be informative to survey this region again and find out if BCs are detected at earlier stages of disease.

As the country develops education initiatives to increase breast awareness among rural women, the findings from our survey of this area will be informative. We found the majority of women were married, Muslim, between the ages of 25 and 49 years, and perceived themselves as of ‘‘medium’’ economic status. The majority of women had children, and approximately 50% were using forms of

contraception. Therefore, opportunities for increasing breast awareness could exist in the clinical setting where women receive gynecologic care. Barriers to seeking breast care may also involve the following: level of education and access to information, perceptions of the female body and breast examination, fears of the diagnostic and treatment interventions, and balancing other family needs, such as being mothers and caregivers [28, 31–35]. Such factors should be considered when developing educational materials with small focus groups to assess the effectiveness of messaging and content.

Evaluating palpable breast masses with ultrasound-guided FNAC offers a cost-effective approach for the early detection of BC in less developed countries that lack routine BC screening programs with mammography [36]. In a low-income country like Ethiopia, where more than three-fourths of the female population is aged <50 years, mammographic BC screening is not recommended [37].

Conclusion

A considerable prevalence of self-reported breast abnormalities of 3.4% among nearly 8,000 women and seven BC cases were found in rural Ethiopia. Only half of the women knew about and only one in eight had practiced breast self-examinations in the past. Only one-third of the women sought formal health care after being aware of abnormal breast changes. Breast awareness campaigns may inform the population. Of seven BC cases, only two had been diagnosed before. The other patients had clinically locally advanced disease, but even after a confirmed diagnosis, only three women opted for care within the health care system. This vicious cycle of late presentation, short survival, and fatalistic attitude in patients must be addressed.

The Ethiopian national cancer control initiatives must respond to the increasing burden of BC in rural and urban areas and address the need for breast examination, diagnostic services, and treatment. Ethiopia's health care system should develop tailored interventions to track BC at an early stage. Initiatives could mobilize groups of BC survivors, who may play an important role to raise awareness, alter negative perceptions, and inform ways to improve care in a complex health care system.

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Breast cancer morbidity and mortality in rural Ethiopia: data from 788 verbal autopsies

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Abstract

Introduction: In Ethiopia, breast cancer is the leading cause of cancer among women. Little is known about the duration of disease and symptoms of patients who died from breast cancer in rural Ethiopia. The objective of this study was to assess breast cancer mortality with a particular focus on the self-reported duration of illness including suffering of symptoms, and need for medical care.

Methods: The cause of death was determined among randomly selected Ethiopian women residing in western Ethiopia. A modified standard verbal autopsy (VA) questionnaire was completed by women whose sisters had died. The questionnaires were reviewed by two independent local physicians to assign a cause of death. We analyzed pattern of cause of deaths, duration of suffering, symptoms, and treatment received.

Result: In our study, the age at death was very similar to other population-based data from Ethiopia. We found 32% of 788 deaths were caused by communicable diseases, 12.1% by neoplasms, and 9.4% by pregnancy/maternal mortality. Breast cancer was the second leading neoplasm, responsible for 21 (2.7%) of all deaths (95% CI 1.5–3.7%), and was among the top five causes of non-communicable deaths. The median age of breast cancer death was 37 years, younger than for other causes of death. The median duration of illness with breast cancer was around 1 year. This was substantially more compared to the duration of infectious diseases, but less than the duration of reproductive neoplasms, diabetes, and epilepsy.

Discussion/conclusion: Breast cancer deaths are common causes of death in women of rural Ethiopia. When assessing the total duration of illness according to specific causes of death, breast and other cancers accounted for a large share of the burden. This has practical implications and highlights the need for palliative care for cancer patients. Substantial efforts are necessary to improve early detection and treatment for breast cancer to reduce premature death in women.

Keywords: Breast cancer, Cause of death, Verbal autopsy, Duration of illness

Introduction

Breast cancer deaths have become recognized as an emerging public health problem in developing countries in the past few decades. Breast cancer is the most frequently diagnosed malignancy among women and the leading cause of cancer death among females worldwide, with an estimated 2.1 million cases and 627,000 deaths in 2018. Worldwide, breast cancer accounted for 11.5% of new cancer cases and 6.6% of deaths due to all cancers in 2018. The age-standardized breast cancer incidence and mortality rates in East Africa are 33.0 and 17.9 per 100,000 women per year, respectively [1].

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There are striking differences in mortality rates from breast cancer in developed and developing countries attributed to late presentation and lack of therapy [2–5]. In most high-income countries, more than 70% of breast cancer patients are diagnosed in stages I and II. However, only 20–50% of patients in the majority of low- and middle-income countries are diagnosed at early stages [6–8]. The majority of breast cancer in women in low-income countries present at an advanced clinical stage, resulting in limited and difficult therapeutic options and contributing to the poor survival rate [6].

In Ethiopia, breast cancer is the leading cause of cancer-morbidity among adult women, accounting for one-third of all cancer cases among women and one in five of all cancer cases [8, 9]. An estimated 16,133 new breast cancer cases and 9061 breast cancer deaths occur annually in the country [1]. Women living in rural areas often seek treatment from traditional healers before seeking help within the formal health system. Only 4.5% of breast cancer patients initially seek care in a cancer hospital, whereas 70% of patients seek care first from a traditional healer or at a primary care site. In contrast, patients who have direct access to local and regional hospitals have the fewest number of encounters for treatment elsewhere [10].

The magnitude of mortality and duration of suffering from illness are important data to understand the burden of disease in a population. But in many low-income countries, no registration on the cause of death occurs due to a lack of medical death certificates or death registry. Verbal autopsy (VA) is a method using a questionnaire to assess details about signs and symptoms preceding the death and a physician's review to conclude a likely cause of death [11]. This is done at sentinel sites to obtain information on mortality within the community. This study used verbal autopsy data to obtain information on the magnitude of breast cancer mortality and the duration of illness, compared to other causes of death in a rural part of Western Ethiopia. This data aims to reflect morbidity and mortality due to breast cancer in rural Ethiopia with a focus on the self-reported duration of the illness considering time with breast symptoms, pain, and under medical care and show the need for specific health services of the disease commonly not considered relevant in the setting.

Methods

Study area and period

For this analysis, data were obtained from three prospective verbal autopsy surveys, conducted between 2011 and 2012 in the West Wellega (Aira, Guliso, Begi, Kondala), Gidami (Kelem) and Bale districts of the Oromia region, Ethiopia, with an estimated 237,222 and 1,402,492 inhabitants respectively [12].

Study design

A community-based cross-sectional study was carried out and modified standard verbal autopsy questionnaires were completed in interviews with randomly selected female relatives who confirmed they had a deceased sister. Structured data collection tools were used to obtain information about the deceased sisters of the respondents [13].

Study population

The study population comprised of all deceased sisters who had died in the 10 years preceding the survey to minimize recall bias. Information was obtained through interviews with their female relatives.

Inclusion and exclusion criteria

All adult female relatives from participants who were at least 15 years old and died in the 10 years preceding the survey in Aira, Guliso, Begi, and Bale were included. Excluded from the analysis were any reported death of women under the age of 15 or any case in which interviewees were unable to describe the symptoms leading to the death of their family member.

Sampling and sampling procedure

All three studies employed a similar approach for gathering data. All female residents in randomly selected clusters were interviewed about their relative's vital status utilizing the Direct Sisterhood Method [14]. If sisters died, caregivers/sisters were how long their female family member suffered from the disease prior to death and which symptoms she experienced.

Sample size

We assumed three in five cancer deaths to be due to breast cancer. Therefore, to detect 3% with a precision of 1.75–4.25%, 800 verbal autopsies were needed [15].

Data collection tools

A standard four-digit VA questionnaire on signs and symptoms, duration of illness, and health service visits was used for data collection [16]. Few modifications to the survey were made with input from an expert medical panel to include detailed breast cancer symptoms. These additional questions were intended to improve the questionnaire's sensitivity towards malignant diseases and to facilitate a differential diagnosis among them.

Operational definitions

The specific cause of death

The cause of death for the completed VA questionnaire was reviewed by two independent physicians who assigned an underlying cause of death. Intra-reviewer reliability was tested for 10% of the sample. A third physician review was added in case of contradicting cause of death.

Unknown cause of death

A death was classified as "unknown cause" when three independent local physicians assigned different causes of death or when the two first physicians classified the cause of death concordantly as "unknown".

A broad category of cause of death

The cause of death was further broadly categorized or grouped using the WHO International Classification of Disease (ICD-10) code [17].

Duration of illness

The period between the date of death and the first manifestation of symptoms, pain, or other suffering from the disease or injury leading to death.

Data quality management and analysis

The collected data were checked for completeness and accuracy and corrected before leaving the household. All data were entered into an electronic database, coded, and checked for missing values, outliers, and inconsistencies. The completed VA questionnaires were reviewed by two independent local physicians to assign three causes of death (underlying, immediate, and contributing factors) according to the WHO International Classification of Disease (ICD-10) code [17]. Differences in diagnoses between these physicians were subsequently reviewed by a third independent physician. The final cause of death bases on the agreement between any of the two physicians.

We performed descriptive statistics to calculate relative and absolute frequencies of causes of death and sociodemographic variables. We report relative frequencies and their 95% confidence intervals (CI) and medians with their interquartile range (IQR).

Results

A total of 4942 women were interviewed and reported on about 21,396 female family members. Of them, 788 (3.7%) died at the age above 15 years between 2001 and 2012 (shown in Fig. 1). The physicians agreed in 67% of

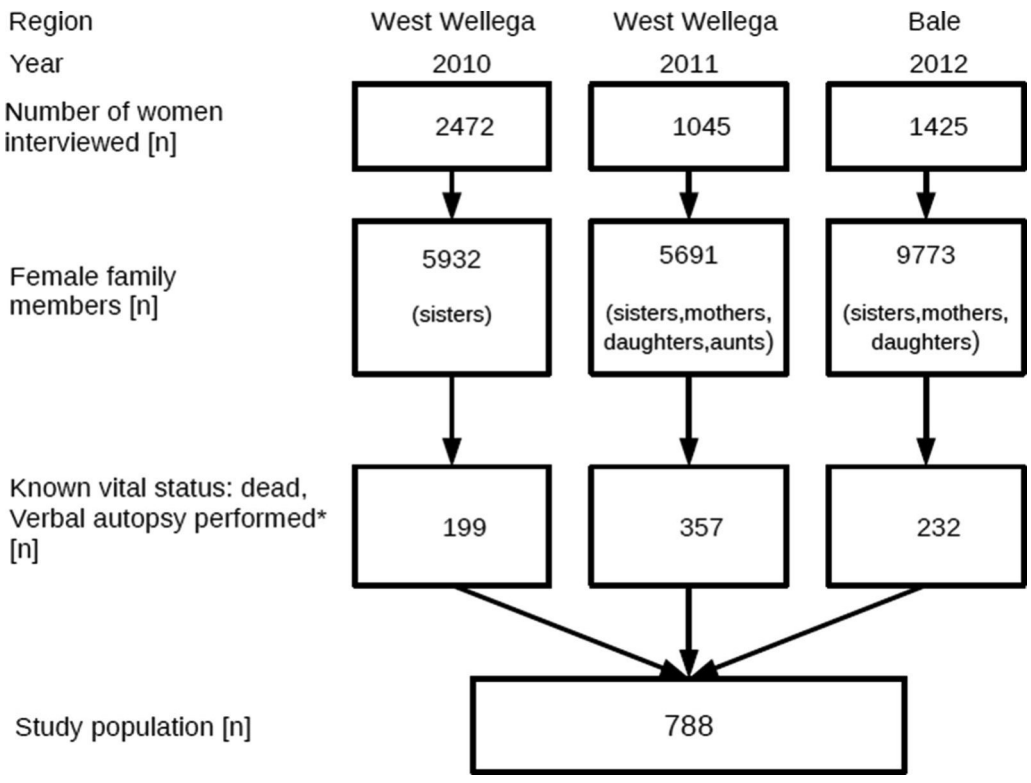

Fig. 1 Consort diagram for study population

the VA code diagnoses, with intra-reviewer reliability of about 72% and 80%.

Socio-demographic characteristics of patients who died from breast cancer

The sample's age distribution (Additional file 1: Table S1) is similar to the age structure of adult women in the Health and demographic surveillance sites (HDSS) in Ethiopia [14]. Thus, we can assume the age distribution of deceased among our study sample is representative compared to other similar studies in Ethiopia (Additional file 1: Table S1). The median age of breast cancer deaths was 37 (IQR 26–45) years, which is substantially lower compared to the median age for deaths from other diseases (with a median of 46 (IQR 32–60) years). A total of 11 (52.3%) breast cancer deaths occurred among women between 15 and 49 years and eight (38.1%) women died in the agegroup between 50 and 64 years. All other socio-demographic information of women who died from breast cancer was comparable to non-breast cancer deaths (Table 1).

Table 1 Socio-demographic characteristics of adult females deceased between 2001 and 2012 in West Welega and Bale regions, Ethiopia, 2013

Socio-demographic variables	Breast cancer cause of death	Non-breast cancer cause of death
	n (%)	n (%)
Age group		
15–24	2 (9.5)	72 (9.4)
25–34	4 (19.0)	128 (16.7)
35–49	5 (23.8)	201 (26.2)
50–64	8 (38.1)	202 (26.3)
65+	2 (9.5)	164 (21.4)
Marital status		
Single	0 (0.0)	49 (6.4)
Married	17 (81.0)	550 (72.1)
Divorced	0 (0.0)	10 (1.3)
Widowed	4 (19.9)	141 (18.5)
Unknown	0 (0.0)	13 (1.7)
Educational status		
Illiterate	16 (76.2)	610 (81.9)
1–8 grade	3 (14.3)	90 (12.1)
9–12	2 (9.5)	43 (5.8)
12+	0 (0.0)	2 (0.3)
Occupation of the deceased		
Housewife or farmer	20 (95.2)	702 (92.2)
Trader	0 (0.0)	11 (1.4)
Employee	0 (0.0)	11 (1.4)
Other	0 (0.0)	22 (3.0)
Unknown	1 (4.8)	15 (2.0)
Place of death		
Home	19 (90.5)	624 (82.2)
Hospital	0 (0.0)	62 (8.2)
Other health facility	0 (0.0)	19 (2.5)
On the way to hospital	0 (0.0)	16 (2.1)
Unknown	2 (9.5)	27 (3.6)
Other	0 (0.0)	11 (1.4)

Causes of death

In total, 32.0% (95% CI 28.7–35.2%) of all deaths occurred due to a communicable disease (Fig. 2). Most frequent specific causes of death were pulmonary tuberculosis (8.8%; 95% CI 6.8–10.7%), diarrhea (5.8%; 95% CI 4.2–7.5%), unspecified infectious diseases (5.7%; 95% CI 4.1–7.3%), malaria (5.2%; 95% CI 3.6–6.7%) and HIV/AIDS (4.3%; 95% CI 2.9–5.7%).

Non-communicable diseases (NCDs) accounted for around 42.1% of deaths (95% CI 38.7–45.6%). Most frequent NCDs were unspecified cardiac (7.5%; 95% CI 5.6–9.3%), stroke (6.1%; 95% CI 04.4–7.8%), digestive neoplasms (3.8%; 95% CI 2.5–5.1%), other unspecified gastrointestinal disorder (3.4%; 95% CI 2.1–4.7%), and breast cancer (2.7%; 95% CI 1.5–3.7%). Another 9.4% (95% CI 7.3–11.4%) of deaths were related to pregnancy and childbirth and 2.9% (95% CI 1.7–4.1%) due to external causes of death (shown in Fig. 2). Differences between the most frequent causes of death between the three studies are summarized in Additional file 2: Table S2.

Breast cancer mortality, other causes of death, and duration of illness

The majority of infectious diseases (such as diarrhea, meningitis and encephalitis, malaria acute respiratory infection) and maternal causes of death had a median duration of illness of fewer than 7 days (Table 2).

In contrast, patients with NCDs suffered for a prolonged time from their illnesses, the longest duration being in the case of reproductive neoplasms (median 730 days), diabetes (730 days), epilepsy (730 days), chronic obstructive pulmonary disease (548 days), HIV/AIDS (365 days) and breast cancer (365 days). Seven in ten women suffered for more than 6 months from breast cancer.

Major reported symptoms and treatment of patients with death due to breast cancer

Around 74% of participants reported that the patient who died from breast cancer suffered from swelling or ulcers in the breast, 63% had a painless lump in the breast, and 47% had breast ulceration and/or inflammation with breast swelling (Fig. 3). About one-fourth of women with breast cancer had bloody nipple discharge.

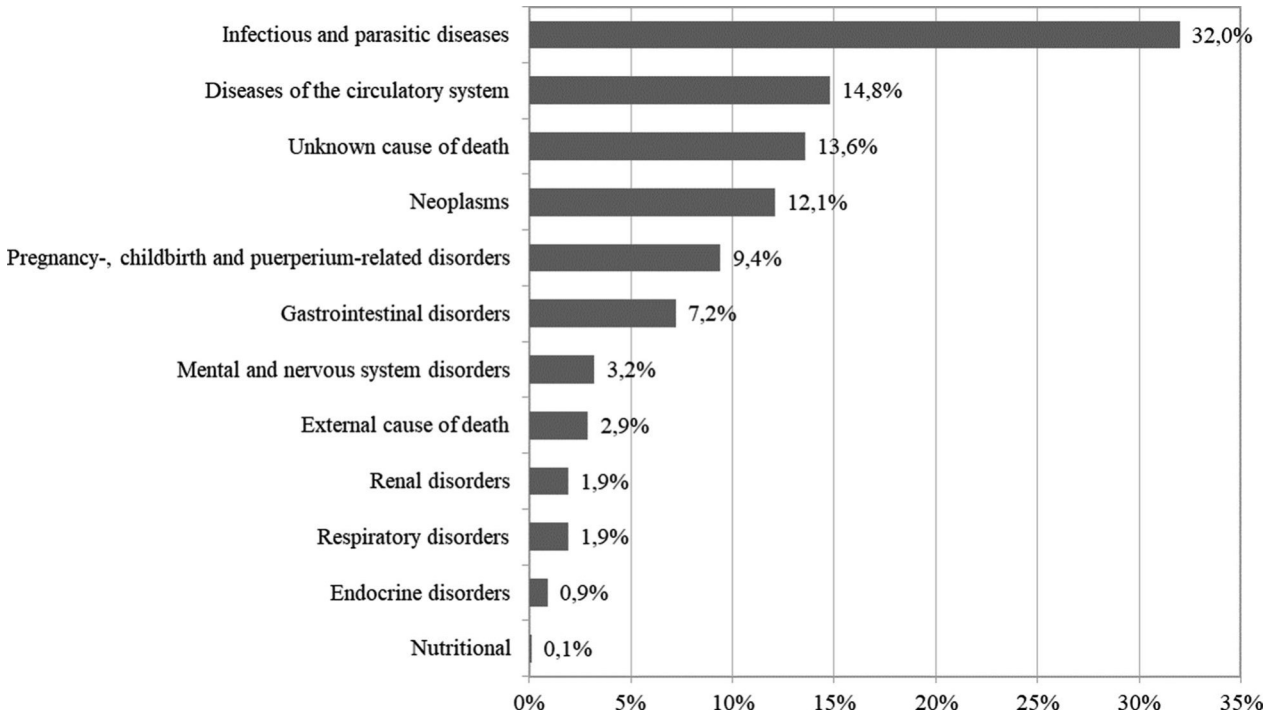

Fig. 2 Adult female broad categories of death in three sites of Oromia, Ethiopia 2010–2012

Regarding general symptoms, 47% of women had weight loss and night sweats, 42% had fever and sweating, and 26% had breathing problems.

Concerning seeking treatment, more than 68% of women with breast cancer were hospitalized at some point and received treatment (details were not specified) before death. About two-thirds of the patients had surgery and 47% had breast surgery or mastectomy. About 37% received antibiotics at some point during their care. Around 90.5% of women who died of breast cancer and 82.2% of women who died of other causes died at home.

Discussion

The main aim of this study was to determine the pattern of breast cancer mortality and other causes of death among adult women in rural Ethiopia using verbal autopsy. We also assessed the duration of illness for each underlying cause of death with special attention to breast cancer morbidity.

In this study, the median age of adult women in rural Ethiopia who died from breast cancer was 37 years, which is considerably younger than the median age at death in this cohort. This age is considered young given the average lifespan of Ethiopian women (at the time of the survey about 61.1 years in 2010 [12]). Other studies revealed high proportions of breast cancer diagnosed in young age groups in Ethiopia, often with a late presentation. Often patients visit traditional healers, lack awareness of existing treatments, and experience delay at health facilities. All these factors negatively influence the prognosis of breast cancer in rural Ethiopia [14, 18]. This study found that the majority of breast cancer deaths occur among women in the reproductive age group. This implies that, in addition to attention on pregnancy- or childbirth-related deaths, awareness needs to be raised regarding breast cancer affecting women in this age group where they are responsible for families and children [16]. We found that breast cancer is the second leading cause of death from neoplasms in women and among the top five causes of death from NCD. Studies from other settings report that breast cancer is the leading cause of cancer death among adult women in developing countries [19, 20].

This study found that, in the rural setting of Ethiopia, NCD accounted for 42% of deaths among women, whereas infectious and parasitic causes of death accounted for 32% of deaths. Several studies align with our findings and have also reported that women in sub-Saharan countries, including Ethiopia, suffer from a double burden of non-communicable and infectious diseases [21–23]. This has implications to increase resource allocation.

The majority of women in this region of Ethiopia died at home (90.5%). This proportion was higher than in a

Table 2 Duration of illness by specific cause of death at three sites of the Oromia region, Ethiopia 2010–2012

Cause of death	# (%)	Rank	Total number of days	Rank of total	Median (days)	IQR (days)
Cause of death unknown	107 (13.6)	1	30,363	1	62	14–365
Other and unspecified cardiac diseases	59 (7.5)	3	26,631	2	180	14–365
Pulmonary tuberculosis	69 (8.8)	2	23,065	3	255	62–365
Epilepsy	17 (2.2)	14	23,049	4	730	60–2190
Stroke	48 (6.1)	4	15,761	5	14	3–180
Reproductive neoplasms	12 (1.5)	19	11,802	6	730	365–1095
HIV/AIDS	34 (4.3)	8	10,489	7	365	61–365
Other unspecified Gastrointestinal disorders	27 (3.4)	11	10,399	8	150	60–700
Breast neoplasms	21 (2.7)	12	9296	9	365	210–730
Mental and nervous system disorders	8 (1.0)	24	8830	10	365	9–2555
Other and unspecified neoplasms	21 (2.7)	13	8661	11	195	16–548
Diabetes mellitus	7 (0.9)	26	7085	12	730	90–1825
Digestive neoplasms	30 (3.8)	10	6935	13	184	121–365
Other and unspecified infection diseases	45 (5.7)	6	6240	14	31	14–167
Renal failure	15 (1.9)	16	5471	15	90	7–365
Liver cirrhosis	14 (1.8)	17	5031	16	365	92–365
Diarrheal	46 (5.8)	5	4120	17	7	7–21
Chronic obstructive pulmonary disease	7 (0.9)	27	2250	18	548	60–1095
Respiratory neoplasms	10 (1.3)	22	1513	19	137	21–240
Other and unspecified maternal CoD	13 (1.6)	18	679	20	2	1–93
Asthma	8 (1.0)	25	459	21	45	3–365
Acute abdomen	16 (2.0)	15	416	22	2	1–7
Malaria	41 (5.2)	7	359	23	6	3–12
Obstetric hemorrhage	33 (4.2)	9	171	24	2	1–3
Acute cardiac disease	10 (1.3)	23	157	25	10	3–20
Acute respiratory infection	12 (1.5)	20	113	26	6	2–14
Pregnancy-related sepsis	7 (0.9)	28	100	27	5	5–15
Pregnancy-induced hypertension	6 (0.8)	29	69	28	12	6–14
Meningitis and encephalitis	5 (0.6)	30	53	29	7	5–7
Obstructed labor	12 (1.5)	21	34	30	2	2–4
Abortion-related death	2 (0.3)	34	17	31	9	3–14
Intentional self-harm	5 (0.6)	32	1	32	0	0–1
Road traffic accident	3 (0.4)	33	1	32	0	0–1
Other and unspecified external CoD	2 (0.3)	35	1	32	1	0–1
Other transport accident	2 (0.3)	36	1	32	0	0–1
Anemia of pregnancy	1 (0.1)	37	1	32	1	1–1
Accidental fall	5 (0.6)	31	0	33	0	0–1

study conducted in Addis Ababa, the capital of Ethiopia, which reported that 71.3% of breast cancer patients died at home. This could be explained by the fact that our study was conducted in a rural setting in Ethiopia where there is an underdeveloped infrastructure, limited health facilities, and low utilization and coverage of health services [24]. Moreover, it has been reported from other African countries such as Nigeria that long waiting times to receive treatment, limited health care resources, and e.g. socio-cultural norms, attitudes, and beliefs explain the observed high rate of women dying at home [25]. We found that most of the participants had undergone breast surgery only. Systemic treatment was not available in rural areas and travelling to Addis Ababa was reported impossible due to financial constraints.

Most women who died from breast cancer had symptoms of their illness for over 1 year prior to their death. In contrast, the median duration of suffering was 7 days or less for communicable diseases like malaria, acute respiratory infection, diarrhea, meningitis, and encephalitis,

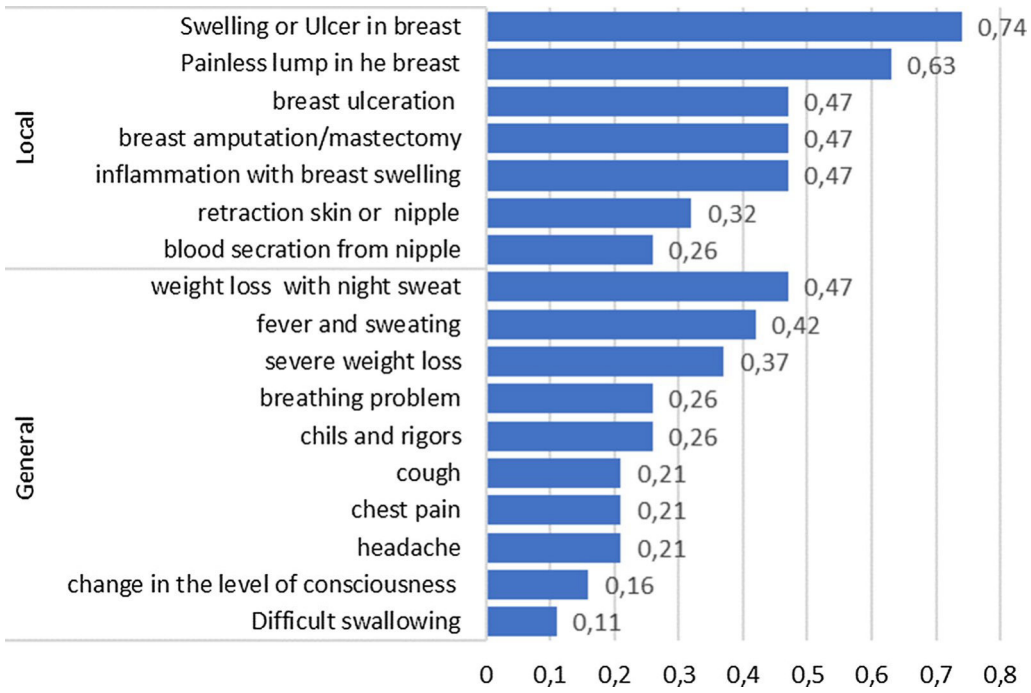

Fig. 3 Major report symptoms of adult women deceased due to breast cancer cause of death

which accounted for 18% of all deaths in the population. The long duration of illness may affect household and community psycho-social and economic status in a number of ways. These may include disrupted family activities and productivity, anxiety or depression, interruption of social networks of support, high out-of-pocket costs for healthcare, and reductions in family savings and investments [26, 27]. These intertwined compounding economic effects can also be felt throughout communities, as within many African cultures, and particularly in Ethiopia, individuals with chronic illness usually receive support from family as well from the surrounding community [28]. Ethiopia made significant changes in maternal-child health and communicable diseases over the last two decades. However, less attention is still given to the prevention and control of noncommunicable diseases. The new Ethiopian cancer control and prevention strategy was drafted in 2016 and includes six new peripheral cancer centers. These centers are still not providing service. Therefore we believe the situation in rural Ethiopia has not changed much since 2012. Study on breast awareness and breast cancer in rural Ethiopia showed a high unmet need for breast care in a rural setting [29].

Strengths and limitations

This is to our knowledge the first study to conduct surveillance in West Ethiopia in a population without previous observation. The physician's review result showed consistency in more than two-thirds of the VA code diagnoses with intra-reviewer reliabilities of about 72% and 80%, which was very similar to previous studies [11]. Additionally, this is the first study to compare the duration of illness in a considerable number of 788 deaths. Although the data is considerably old, it still presents the burden of breast cancer in a rural setting without access to a cancer center. The study had also some limitations, as sisters, mothers, and aunts were asked about a wide range of signs and symptoms that led to death in the last 10 years, which might have introduced recall bias. To avoid making relatives anxious, some patients may have not disclosed their symptoms to close family members.

We detected 13.6% of cases with an unknown cause of death, other studies reported around 10% unknown cause of death. Reliability and repeatability towards interpreting the VAs and assigning causes of death by physicians could be mentioned as a limitation but various other studies have used this methodology [30].

Conclusion and recommendations

Non-communicable diseases including breast cancer are among the leading causes of women's death in rural Ethiopia, breast cancer frequently occurs in a young reproductive age group, and results in a long duration of illness. These findings are an indication for more efforts to prevent non-communicable causes of death among women, in addition to infectious and maternal causes.

The Ministry of Health should scale up preventive and curative interventions in rural parts of the country. The long duration of illness shows the urgent need for palliative care for cancer patients in rural areas. Substantial efforts are necessary to improve early detection and access to care for breast cancer patients to reduce suffering and premature deaths. Governmental and non-governmental organizations and health care providers should give serious attention to developing and implementing adequate breast cancer services within the primary health care system.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-022-01672-7.

Additional file 1. Age structure used on the study's population compared to those of documented deaths at Kersa Health and Demographic surveillance site of Ethiopia.

Additional file 2. Top leading specific cause of death in three site of Oromia, Ethiopia 2010-2012.

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Authors' contributions
WA, AW, SU, AA and EJK conceptualized the study, performed formal data analysis, investigation, methodology, software, validation, and visualization. AF and GAB acquired the data, and administered the project. FF and LT contributed to methodology and visualization. WA wrote drafted the manuscript. EJK acquired funding, resources, administered and supervised the work. All co-authors reviewed, edited and approved the draft. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from Addis Ababa University Ethical Review Board, Ethiopia (032/2011) and Martin-Luther University Ethical Review Board, Halle, Germany (23.8.2010). All methods were carried out in accordance with relevant guidelines and regulations (Declaration of Helsinki). All individuals were asked for informed consent prior to the interviews, if subjects were under 16 or dead, informed consent from a parent and/or legal guardian/next of kin was obtained.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Characteristics and follow-up of metastatic breast cancer in Ethiopia: A cohort study of 573 women

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ABSTRACT

Objectives: There is little information on characteristics, treatment and outcome of metastatic breast cancer (mBC) patients in low-income countries. This study aims to describe mBC in the setting of Ethiopia.

Materials and Methods: A retrospective cohort study was conducted among all female mBC patients from the only oncologic hospital in Addis Ababa 01/2006 to 12/2010. Time between first metastasis and known death or loss to follow-up for more than six months as surrogate for death were used for Cox proportional hazards model.

Results: A total of 573 patients were included; 188 (32.8%) women with de novo mBC (dnmBC) and 385 women with recurrent mBC (rmBC). The average age at time of first metastasis was 43.7 (standard deviation 11.9) years with an average survival probability of twelve months. Negative hormone receptor status, only present in 29% (Hazard ratio HR = 2.28 [95% confidence interval CI 1.56–3.32] $p < 0.001$), and grade 3 (HR = 1.72 [95% CI 1.15–2.55] $p = 0.008$) had significant influence on survival. Patients with initial bone metastasis (HR = 0.63 [95% CI 0.48–0.83] $p = 0.001$) had best chances of survival compared to more common initial visceral metastasis. About 35% of the patients received chemotherapy and 30.5% were on endocrine therapy.

Conclusion: The lower survival for mBC in Addis Ababa compared to that from Western countries is presumably due to the later presentation at the hospital and lack of standard therapy. An unexpected high proportion of patients with hormone receptor positive mBC encourage consequent utilization of endocrine therapy to improve the quality of palliative care in this cohort.

1. Introduction

Breast cancer (BC) is the most common cancer in women worldwide. About 1.7 million newly diagnosed cases are registered every year [1]; it accounts for about 521,900 deaths annually. With increasing life expectancy, non-communicable diseases like BC are also becoming a relevant issue in less developed regions as it is the most frequent cause of cancer death in women in these regions (about 325,000 deaths annually) [2]. Stage at time of diagnosis is strongly associated with survival rate from breast cancer. Meta-analyses show that the percentage of late-stage disease at the time of the diagnosis is still high in Sub-Saharan Africa [3,4]. Most patients present with locally advanced tumours which presumably often have non-detected metastasis as modern staging procedures

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are not standard.

Even though metastatic breast cancer (mBC) remains incurable [5], it is crucial to have detailed knowledge about the tumour biology for individualized therapy [6–8]. Drugs like tamoxifen are nowadays available worldwide, whereas therapeutic innovations such as the targeted therapy with trastuzumab is not readily available in low resource countries [9], despite the fact that it has resulted in modest improvements in survival rates [10–12] and is included in the list of WHO essential medicines [13]. There is little information on clinical characteristics, treatment and outcome of patients with metastasis in low-resource countries [14]. A retrospective study from Nigeria [15] had a mean overall survival (OS) of 17.5 months in mBC patients. Liver and lung seem to be more common sites of metastasis than bone or brain according to a study from Morocco [16].

With almost 102 million inhabitants, Ethiopia is the country with the second largest population in Africa and it is also one of the ten poorest countries in the world with regard to BIP/capita [1]. Only 19.5% live in urban areas compared to e.g. Germany with 75%. The life expectancy of Ethiopian women is 66.8 years compared to 83.4 years of German women [17]. Health expenditure is 4.9% of GDP and 11.3% in Germany [18]. Almost 42 per 100,000 Ethiopian women suffer from BC with a mortality of 23 per 100,000 [19] (see Fig. 1).

Based on the World Health Organization's global cancer control strategy, the Federal Ministry of Health in Ethiopia set up a “National Cancer Control Plan 2016–2020” [20] for the first time to reduce cancer incidence and mortality [21]. Central strategies are promotion of breast self-awareness as well as training of clinical breast examination for health workers in order to detect BC at an early stage suitable for curative treatment.

This study aims to describe mBC in Ethiopia to point out the needs for improving patient palliative treatment in low-resource countries. Our primary objective was to assess the influence of prognostic factors at time of metastatic diagnosis on survival in mBC. We determined survival time of women with mBC and the types of therapy used in this setting. Assuming that access to the standard treatments was very limited in the country, we expected to find short survival times in mBC patients. Additional specific hypotheses of this study included: mBC patients have poor prognostic markers such as young age, high tumour grade, high tumour load and hormone receptor negative tumours – this leads to poor survival; patients with de novo mBC (dnmBC) have better chances of survival than patients with metastasis during follow up (recurrent mBC, rmBC), assuming a larger variety of adequate treatments; survival rate of patients with bone metastasis is better than that of patients with visceral metastasis; survival of mBC patients who receive treatment is better than for untreated patients; patients with mBC receive only a limited number of therapies, mainly based on endocrine and chemotherapy.

2. Material and methods

2.1. Patient population and data collection

Breast cancer cases were requested from the Radiotherapy Centre at Addis Ababa University Hospital, Ethiopia. It is the only centre offering oncologic therapy for BC patients in Ethiopia. In the study, we included all female patients with invasive breast cancer and evidence of metastatic disease treated at the centre between January 2006 and December 2010 [22]. Analysis of patients without evidence of metastatic diseases [23] and analysis of hormone receptor status of all patients has been reported before [22]. The patients were treated in accordance with the Breast Health Global Initiative guidelines [24] and based on the available treatments on site. During that time anthracyclines were purchased centrally by the government for use in the radiotherapy centre. There had not been an initiative to improve access to chemotherapy yet.Information was collected concerning age, menopausal status at diagnosis, parity, use of contraceptives, breast cancer stage, type of initial therapy such as surgery, chemotherapy and endocrine therapy, time of diagnosed metastasis, site of metastasis, type of palliative therapy. Patients with positive or unknown hormone receptor status, as tested in the local pathology laboratory, received free endocrine therapy which was funded by a grant from AstraZeneca to the Axios Foundation to improve breast cancer care by developing a centre of excellence at Addis Ababa University. HER2-status was not tested in this study.

2.2. Statistical analysis and variable definition

Primary endpoint was reported death or loss to follow-up (LTFUP). For logistic reasons, vital status was rarely obtained. Patients were considered LTFUP when more than 6 months passed

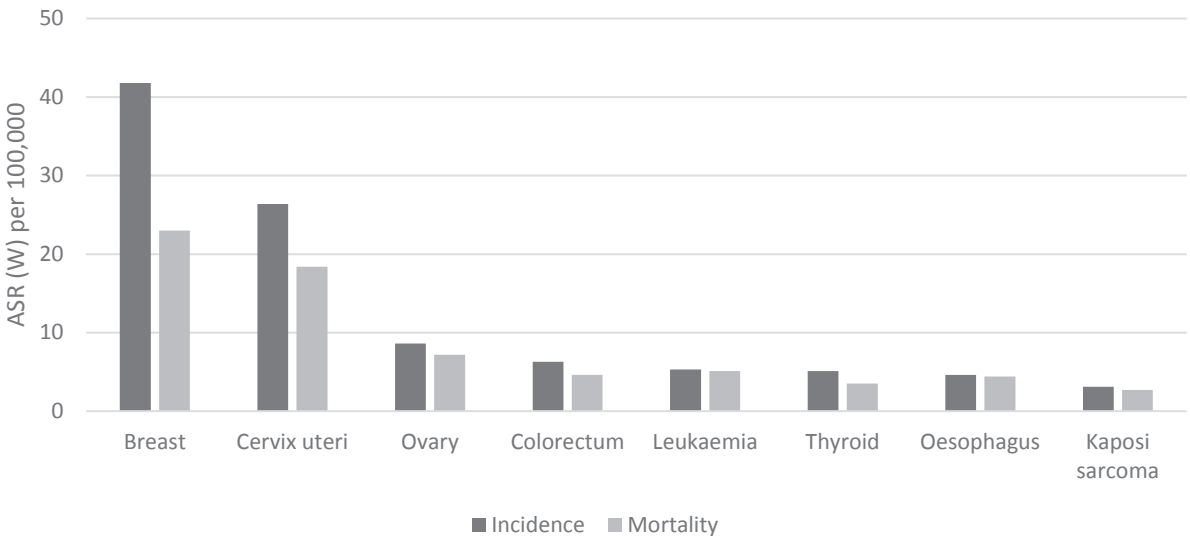

Fig. 1. Estimated age-standardised incidence and mortality rates in Ethiopian women (ASR per 100,000) [19].

since their last appointment since follow-up visits were recommended in three to six month intervals. Patients LTFUP were assumed dead; we used the time of first metastasis until LTFUP as a basis for survival estimates. This indicates the worst-case scenario of survival.

Patients were grouped according to first site of metastasis. In case of multiple metastases, the most severe was assigned (brain over visceral over bone over skin/lymph node).

SPSS Statistics v24 was used to perform data analysis. Data was analysed using the Kaplan-Meier curve defining certified death as well as LTFUP as an event stratified by hormone receptor status and grading of tumour, site of metastasis and type of palliative therapy. The influences of age, stage and hormone receptor status on outcome were assessed using the proportional hazards model. Cluster stratification was used for the Cox regression in order to minimize variability. The results of the final model were reported using Hazard Ratio (HR) and 95% confidence intervals (CI) and P-value $p < 0.05$ was considered significant.

3. Results

3.1. Patient and tumour characteristics

Out of the 2031 registered BC patients who presented at the Radiotherapy Centre at Addis Ababa University Hospital between 2006 and 2010, paper files of 1672 patients were available. Of these patients, 573 fulfilled the inclusion criteria. Out of total, 290 patients (60.7%) were Addis Ababa residents and 188 patients (39.3%) lived in rural areas. There were 91 patients (19.0%) nulliparous, 146 patients (30.5%) had one or two children, 136 patients (28.5%) were multipara and 105 (22.0%) had more than five and up to 13 children. Most patients were normal or overweight. Underweight led to poor prognosis. The left breast was affected in 267 cases (47.7%), whereas the right breast was affected in 252 cases (45%) As a clinical sign, ulceration was described in 108 patients (18.9%), peau d'orange in 31 (5.4%), inflammation in 15 (2.6%) and infiltration of the chest wall in 13 (2.3%). Multiple tumours were detected in 11 patients (3.2%). There were 6.8% with initially pT1 tumour, mainly grade 2 (61.4%), 91.6% with involved lymph nodes. Invasive ductal histology was seen in 72.6% of patients (see Table 1). Of the 40% with known hormone receptor status, 71% were hormone receptor positive. Her2neu status was not tested in this setting. Mastectomy was the most common surgery, of the 220 cases with information available, 41.4% had pathologically involved margins versus 58.6% free margins.

Death was certified only in 3.4% (19 patients), 59.3% (340 patients) had missed follow-up visits for more than 6 months (therefore included in the group assumed dead, primary endpoint). Median estimated OS with metastasis was 11.7 months (SD = 15.8, range 0–138 months).

The majority of patients (380 patients; 66.3%) presented with visceral metastases, which included lung, pleura and liver. Bone metastases were present in 127 cases (22.2%). Less common were metastases in the brain (19 patients; 3.3%), skin or other sites such as distant lymph nodes (47 patients; 8.2%).

A high number of patients did not receive any cancer-directed treatment (284 patients), especially those patients who developed metastasis during follow up (64.8% vs. 19.1%). There were 7 patients who underwent surgery without any further treatment (see Table 2). However, no information was available concerning receipt of radiotherapy. Initial chemotherapy was mainly anthracycline-based (121 patients; 95.3%) whereas in rmBC, platinum based chemotherapy was often administered (69 patients; 74.2%). Other options included CMF scheme (5 patients; 2.3%), taxanes (1 patient; 0.5%), vinblastine and vinorelbine (4 patients; 1.8%).

Tamoxifen was the main endocrine treatment option for dnmBC (86.6%) whereas aromatase inhibitors were endocrine treatment of choice in patients with rmBC (84.4%).

3.2. Survival estimates

The estimated mean OS with metastasis was 11.7 months (range from 0 to 138 months, median 6.6 months). DnmBC was associated with better prognosis (HR = 0.76 [95% CI 0.61–0.95] $p = 0.014$) in bivariate analysis, mean 14.6 months, median 9.1 months) compared to rmBC (mean 10.2 months, median 5.2 months, see Fig. 2).

Patients with primary hormone receptor positive mBC had better prognosis as well as patients with grade 1 or 2 tumours (see Fig. 3).

High grading of the initial tumour (HR = 1.72 [95% CI 1.15–2.55] $p = 0.008$), negative hormone receptor status (HR = 2.28 [95% CI 1.56–3.32] $p < 0.001$), rmBC versus dnmBC (HR = 1.32 [95% CI 1.05–1.64] $p = 0.014$), visceral versus bone metastasis (HR = 1.59 [95% CI 1.20–2.08] $p = 0.001$) were associated with shorter overall survival, whereas palliative endocrine based treatment (alone: HR = 0.44 [95% CI 0.31–0.63] $p < 0.001$; in combination with chemotherapy HR = 0.33 [95% CI 0.24–0.46] $p < 0.001$) was identified as good prognostic factors in simple regression analysis (Table 3). In rmBC, disease free interval was not a significant prognostic factor (HR = 0.99 [95% CI 0.76–1.29] $p = 0.922$). Table 3 also shows the multiple Cox regression adjusted according to age at first metastasis, body mass index, initial grading, hormone receptor status, time of metastasis appearance, site of metastasis and palliative treatment. In the multiple regression analysis, high grading (HR = 1.85 [95% CI 1.24–2.77] $p = 0.003$), negative hormone receptor status (HR = 1.72 [95% CI 1.17–2.54] $p = 0.006$) and visceral metastasis (HR = 1.56 [95% CI1.18–2.08] $p = 0.002$) indicated a more favourable survival as significant and independent prognostic factors. Endocrine treatment (only: HR = 0.52 [95% CI 0.35–0.77] $p = 0.001$); sequential to chemotherapy: HR = 0.34 [95% CI 0.23–0.49] $p < 0.001$) were associated with better overall survival.

4. Discussion

This is the first detailed and largest study of metastatic breast cancer patients in Ethiopia.

4.1. Socio-demographic and clinical characteristics

In this Ethiopian cohort, the distribution of tumour characteristics of BC such as histological type (mainly non-special type), grading (mainly undifferentiated), presence of hormone receptors and positive family history were comparable to Western setting [25,26] and also to other African studies in the published literature [14,23,27–29]. Although about 20% of inhabitants in Ethiopia live in an urban setting, they counted for 60% of the mBC cases in this study. This could be due to the high costs of transport to the capital city, which leads to inaccessibility to adequate treatment and low compliance of rural patients who are often poor. Age at BC diagnosis and metastasis about 42 (44) years is low. Other studies from Sub-Saharan Africa report similar data, such as Nigeria, where the mean age is 45.9 years with a range from 20 to 81 years [15]. These countries have a high proportion of young people. In Germany, mean age at diagnosis is 64 years [30]. Diagnosis of BC is mainly in the last third of life, considering the fact that life expectancy at birth in Ethiopian women is 67 years and in Germany as well as in other western countries 84 years [17].

Table 1
Socio-demographic, clinical and pathological characteristics of the patients.

	All patients $n = 573$ (%)	dnmBC $n = 188$ (%)	rmBC $n = 385$ (%)
Age at breast cancer diagnosis	18.3–79.4 yrs (42.2 ± 11.8[a])	23.9–79.4 yrs (45.4 ± 12.4[a])	18.3–76.9 yrs (40.6 ± 11.1[a])
Age at first metastasis	20.0–80.0 yrs (43.7 ± 11.9[a])	23.9–79.4 yrs (45.4 ± 12.4[a])	20.0–80.0 yrs (42.8 ± 11.6[a])
<45 yrs	330 (57.6)	95 (50.5)	235 (61.0)
≥45 yrs	243 (42.4)	93 (49.5)	150 (39.0)
Body mass index	13.1–38.8 (23.5 ± 4.7)	13.1–37.7 (22.1 ± 4.9)	20.0–38.8 (24.6 ± 4.5)
<19 (underweight)	70 (18.8)	35 (31.3)	35 (13.5)
19-30 (normal/overweight)	266 (71.5)	71 (63.4)	195 (75.0)
>30 (obese)	36 (9.7)	6 (5.4)	30 (11.5)
Unknown	201	76	125
Residence			
Urban	290 (60.7)	90 (58.8)	200 (61.5)
Rural	188 (39.3)	63 (41.2)	125 (38.5)
Unknown	95	35	60
Family history of breast cancer			
No	436 (92.2)	143 (92.3)	293 (92.1)
Yes	37 (7.8)	12 (7.7)	25 (7.9)
Unknown	100	33	67
Tumour size			
pT1	17 (6.8)	1 (2.8)	16 (7.5)
pT2	93 (37.2)	11 (30.6)	82 (38.3)
pT3	86 (34.4)	8 (22.2)	78 (36.4)
pT4	54 (21.6)	16 (44.4)	38 (17.8)
Unknown	323	152	171
Grading			
G1	30 (14.3)	9 (20.9)	21 (12.6)
G2	129 (61.4)	25 (58.1)	104 (62.3)
G3	51 (24.3)	9 (20.9)	42 (25.1)
Unknown	363	145	218
Involved lymph nodes			
pN0	16 (8.4)	0 (0)	16 (9.2)
pN1-3	174 (91.6)	17 (100.0)	157 (90.8)
Unknown	383	171	212
Histology			
Ductal, non-specified type	414 (72.6)	131 (70.1)	283 (73.9)
Lobular	27 (4.7)	6 (3.2)	21 (5.5)
Other	129 (22.6)	50 (26.7)	79 (20.6)
Unknown	3	1	2
Hormone receptor status			
Positive	164 (71.0)	68 (78.2)	96 (66.7)
Negative	67 (29.0)	19 (21.8)	48 (33.3)
Unknown	342	101	241
Events	359 (62.6%)	118 (62.8%)	241 (62.4%)

[a] Median and standard deviation; dnmBC, de novo metastatic breast cancer; rmBC, recurrent metastatic breast cancer.

Table 2
First-line palliative treatment.

	All $n = 573$ (%)	dnmBC $n = 188$ (%)	rmBC $n = 385$ (%)
Surgery only	7 (1.2)	7 (3.7)	0 (0)
CT ± surgery	106 (18.6)	46 (24.5)	60 (15.7)
ET ± surgery	78 (13.7)	29 (15.4)	49 (12.8)
ET + CT ± surgery	96 (16.8)	70 (37.2)	26 (6.8)
No therapy received	284 (49.7)	36 (19.1)	248 (64.8)
Unknown	2	0	2

dnmBC, de novo metastatic breast cancer; rmBC, recurrent metastatic breast cancer; CT, chemotherapy; ET, endocrine treatment.

4.2. Site of metastasis

Consistent with a study from Nigeria [15] that reported mainly visceral metastasis, followed by bone metastasis and a few cases with metastasis of the central nervous system, we saw also mainly visceral metastasis and only rarely brain metastasis. In Western settings, bones are the most common sites detected clinically and via autopsy followed by visceral metastasis [25,31]. One explanation for that difference is the diagnostic imprecision. Since, due to high costs and lack of therapeutic consequence, only very few MRI or CT examinations are done, many brain metastases are probably not diagnosed. Lack of bone scintigraphy will probably underestimate the proportion of patients with asymptomatic bone metastases. Differential diagnosis e.g. tuberculosis in developing countries is possibly a major confounder due to higher incidence and thus also leads to undiagnosed lung metastasis. Another point is the frequency of staging examinations. Due to the fatal outcome, most patients will not invest in additional imaging to detect other metastases once diagnosed with a metastasis.

4.3. Survival

The estimated mean OS of women with BC metastasis was 11.7 months. This outcome seems to be poorer than data showed from Nigeria [15] with a mean OS of 17.5 months. European authors described median OS of less than two years [p 548 of 32]) and only better survival of about 3.5 years, if remission is reached due to endocrine therapy. Over time *Sundquist* et al. report an increase in median OS in Europe during the past 25 years from 13 to 33 months [12]. The low mean OS in our cohort might be due to two important factors: one is the late detection of metastasis (shifting the starting point-lead time bias) shortening survival duration and the other is

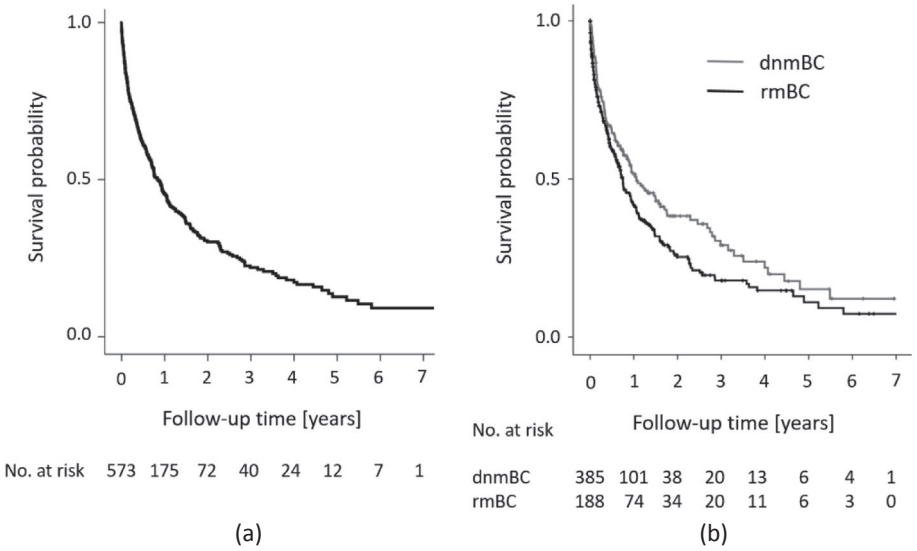

Fig. 2. Kaplan-Meier plot of overall survival probabilities (a-all; b-separate lines for de novo and recurrent metastatic breast cancer); dnmBC, de novo metastatic breast cancer; rmBC, recurrent metastatic breast cancer.

possibly lack of treatment options in the low resource setting. A bias could result from the lack of death certificates. Our surrogate parameter "abrupt loss to follow up" leads to shorter estimates regarding survivals than there probably are (worst-case scenario). But we assume that this bias is small since notes in the file often indicated bad general condition of patients who had not subsequently returned.

4.4. De novo and recurrent mBC

Many studies separate prognostic groups based on timepoint of metastatic appearance. A recently published population-based French study of more than 600 mBC patients [25] did not find any difference, but with a trend to poorer outcome of rmBC patients.

In our cohort, survival was significantly better if metastasis was seen at initial BC diagnosis than during follow up. It is suggested that patients with distant metastasis at initial BC diagnosis have a better prognosis because their disease is therapy-naïve and thus less likely to show resistance to first systemic palliative therapy.

4.5. Survival and site of metastases

Although bone metastasis can cause considerable morbidity and reduced quality of life due to pathological fractures, spinal cord compression and hypercalcaemia, prognosis in of bone metastasis in our cohort was more favourable compared to other sites of metastases. This finding is in line with previous studies both in developed and developing countries [6,10,33,34]. Additionally, *Marshall* et al. demonstrated age at metastasis and histological subtype as independent prognostic factors of French mBC patients [25] with better prognosis seen in older patients and G1 and G2 tumours. Our data is in line with less aggressive tumour biology showing longer survival.

4.6. Survival and age

We did not find differences of survival among different age groups. From Morocco, *Boufettal* et al. [16] also reported comparable prognosis independent of age. The age cut to differentiate between younger and older age differs from 65 years in e.g. a French study [25] to 35 years in a trial from Morocco [16]. In other publications, stratifications of multiple age spans are used so the comparison is difficult - also keeping in mind that life expectancy highly differs in the different countries.

4.7. Treatment

The intention of early BC treatment is to cure patients, whereas the intention of mBC treatment is symptom control with minimal side effects. Management is based on clinical and pathological features of the tumour, previous therapies and decision of the patient. International guidelines recommend endocrine treatment as the treatment of choice in hormone receptor positive mBC, whereas chemotherapy in mBC is used if remission pressure is high or in hormone receptor negative mBC [9,11,35–37]. This has not changed in the past decade [38]. One of the interesting findings of our study was the high percentage of patients where chemotherapy was administered in addition to endocrine treatment. Taxanes, one of the leading agents in Western settings, was only used once, but Platinum, an important agent in triple negative BC, was the agent of choice in rmBC. Diagnostic procedures rarely included HER2 status and often even hormone receptor status. Aromatase inhibitors, bone targeting agents, immunotherapy like trastuzumab were rarely administered despite presence on the WHO essential medicines list. Therapeutic cost is still a major obstacle to implementing state-of-the-art oncologic therapy in a setting of many competing health priorities. A collaboration of the American Cancer Society, Clinton Health Access Initiative, Pfizer Inc. and Cipla Inc. set up an agreement just recently in year 2017 to offer 16 common chemotherapeutic drugs at low costs in order to expand access in Sub-Saharan African countries [39].

4.8. Patients without treatment

There was an extraordinary high proportion of patients that did not receive any treatment at all (50%), especially in rmBC - even though endocrine treatment was free of charge in this setting. This was probably due to the difficult economic situation of the patients who were even unable to travel to the hospital. Also most patients

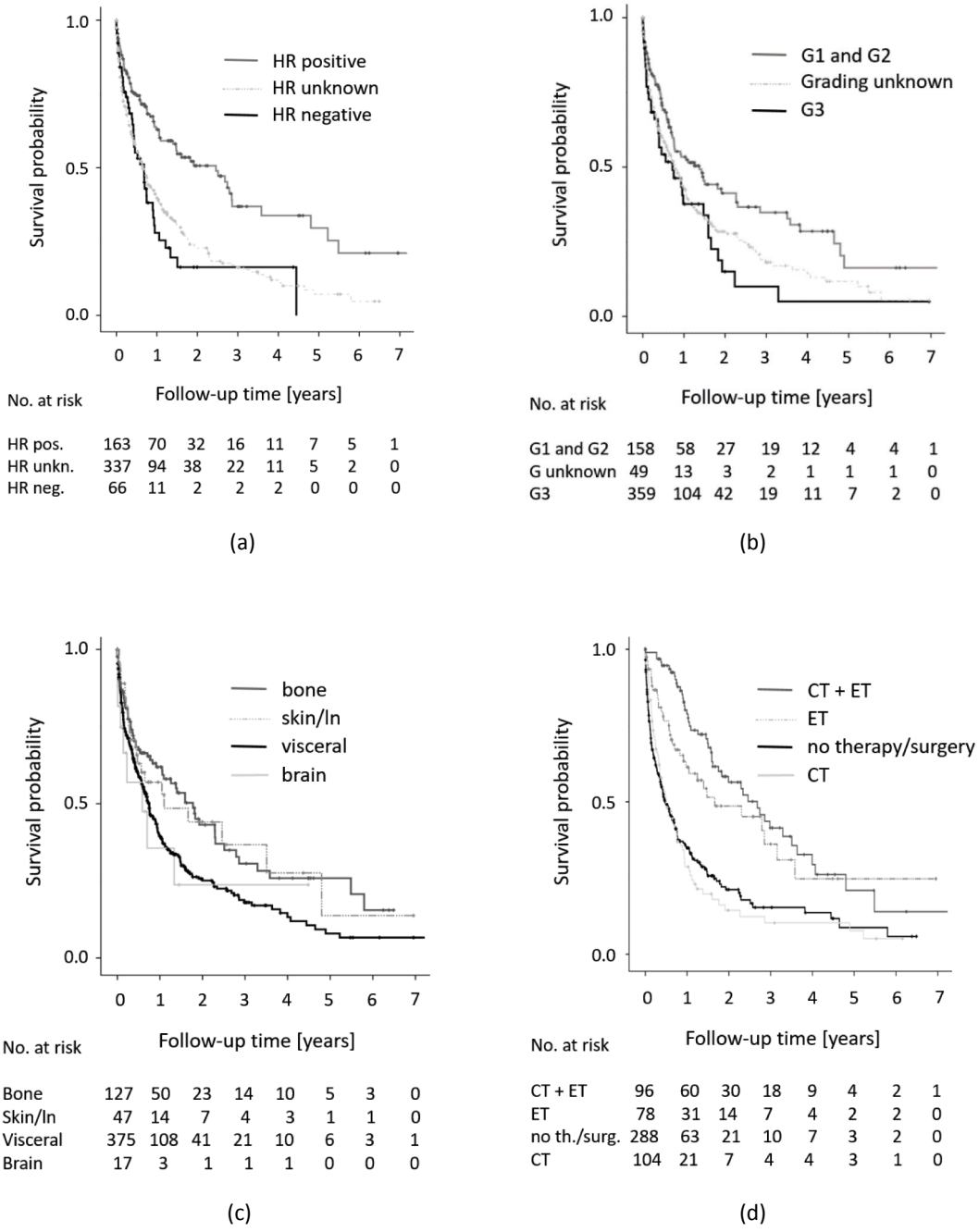

Fig. 3. Kaplan-Meier plot of overall survival probabilities according to initial hormone receptor status (a), grading (b), site of primary metastasis (c) and type of palliative treatment (d); HR, hormone receptor; ln, lymph node; CT, chemotherapy; ET, endocrine treatment.

with rmBC have progressed while on hormonal therapy and the waiting time for chemotherapy at the Hospital is long. Keeping in mind that this is a retrospective study, we additionally expect underreporting of endocrine treatment due to incomplete documentation.

4.9. Limitations

Some limitations need to be mentioned. One major limitation is the lack of actual mortality data but using discontinuation of care as surrogate marker. We suspect a potential survival-time bias, not being able to distinguish exactly between discontinuing follow-up visits due to death or discontinuing follow-up visits due to other reasons. Local colleagues suggest that discontinuation due to death is the most likely reason. It may be possible that e.g. patients receiving endocrine treatment free of charge were more likely to attend follow up visits, whereas patients having to pay for requiring other treatments were less likely to regularly attend follow-up visits once their financial limit was reached. Thus survival of those was possibly underestimated.

For logistic reasons, we were unable to obtain data on radiotherapy. We assume it was rarely offered due to the fact that there was only one radiotherapy machine in the entire country. Similarly, a Nigerian study reported that of all patients referred, only a quarter

Table 3
The simple and multiple Cox regression model in patients with mBC; multiple regression adjusted for age at first metastasis, body mass index, initial grading, hormone receptor status, time of metastasis appearance, site of metastasis and palliative treatment.

Characteristic	Simple regression		Multiple regression	
	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*
Age at diagnosis				
<45 years vs. ≥ 45 years	1.16 (0.93–1.44)	0.204		
Age at first metastasis				
<45 years vs. ≥ 45 years	1.11 (0.87–1.41)	0.421	0.97 (0.75–1.26)	0.844
Body mass index				
underweight vs. normal weight	1.18 (0.86–1.62)	0.304	0.99 (0.72–1.37)	0.964
obese vs. normal weight	0.92 (0.58–1.48)	0.743	0.87 (0.53–1.41)	0.558
Residence				
urban vs. rural	0.82 (0.56–1.20)	0.305		
Initial tumour size				
pT1/2 vs. pT3/4	1.09 (0.78–1.53)	0.617		
Grading				
grade 3 vs. grade 1 or 2	1.72 (1.15–2.55)	0.008*	1.85 (1.24–2.77)	0.003*
Hormone receptor status				
negative vs. positive	2.28 (1.56–3.32)	<0.001*	1.72 (1.17–2.54)	0.006*
Time of metastasis appearance				
rmBC vs. dnmBC	1.32 (1.05–1.64)	0.014*	0.92 (0.61–1.37)	0.663
Site of first metastasis				
visceral vs. bone	1.59 (1.20–2.08)	0.001*	1.56 (1.18–2.08)	0.002*
visceral vs. brain	0.87 (0.49–1.69)	0.690	1.16 (0.59–2.33)	0.651
visceral vs. skin/lymphnode	1.47 (0.97–2.22)	0.071	1.33 (0.87–2.04)	0.193
Palliative treatment				
ET based vs. surgery/no th.	0.44 (0.31–0.63)	<0.001*	0.52 (0.35–0.77)	0.001*
CT based vs. surgery/no th.	1.03 (0.79–1.33)	0.849	0.94 (0.70–1.27)	0.693
ET + CT vs. surgery/no th.	3.03 (2.17–4.17)	<0.001*	2.94 (2.04–4.35)	<0.001*

HR, Hazard Ratio; CI, Confidence Interval; ET, endocrine treatment, CT, chemotherapy; dnmBC, de novo metastatic breast cancer; rmBC, recurrent metastatic breast cancer; *, statistically significant.

of them actually received radiotherapy [15]. This was explained by long waiting lists, financial constraints and organisational difficulties encountered at the centre. Similar circumstances were probably present in Ethiopia.

5. Conclusion

To our knowledge, this is the first study to report on presentation, treatment and outcome of patients with mBC in Ethiopia, Sub-Saharan Africa. A relatively high number of dnmBC cases was probably the result of late stage presentation of cancer patients in Ethiopia. Awareness campaigns would hopefully reduce the proportion of these patients and shift patients towards curable disease. Seeing a mean overall survival of twelve months in our cohort with limited treatment indicates need for adequate availability and quality of palliative care service for breast cancer patients in Ethiopia. Holistic care is essential, especially considering the young age of these patients who are often responsible for the rest of the family. Improving access to modern therapy would probably increase survival of these patients.

Conflicts of interest

The authors declare no conflict of interest.

Ethical approval

Ethical approval from Addis Ababa University Medical Review Board had been obtained.

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RESEARCH ARTICLE

Health system cost of breast cancer treatment in Addis Ababa, Ethiopia

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Abstract

Background

Breast cancer is the leading cancer among women with an annual crude incidence of 27.4 per 100,000 in Ethiopia. The aims of this study were to (a) estimate the unit cost of breast cancer treatment for the standard Ethiopian patient, (b) identify the cost drivers, (c) project the total cost of breast cancer treatment for the next five years, and (d) estimate the economic burden of the disease in the main specialized tertiary hospital—Tikur Anbessa Specialized Hospital (TASH) Addis Ababa.

Methods

Primary data were collected from health and non-health professionals. Secondary data were collected from patient's charts and official reports from various national and international organisations including data from TASH. To establish work-time estimates, we asked professionals on their time usage.

Result

A total of US$ 33,261 was incurred to treat 52 Addis Ababa resident female breast cancer patients in TASH between July 2017 and June 2019. The unit cost of treatment for a hypothetical breast cancer patient to complete her treatment was US$ 536 for stage I and US$ 705 for stage II and III using the existing infrastructure. This cost increased to US$ 955 for stage I and US$ 1157 for stage II and III when infrastructure amortization was considered. The projected total costs of breast cancer treatment in TASH is between US$ 540,000 and US$ 1.48million. However, this will increase to US$ 870,000 and US$ 2.29 million when the existing fixed assets are changed.

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Conclusion

The economic burden of breast cancer treatment is high compared to the economic status of the country. Thus, it is recommended that TASH should revise its charges and breast cancer should be included in the Social and Community based health insurance scheme.

JEL classification: H51, H75, I18, P46

Introduction

Breast cancer is a disease that is manifested when cells in the breast grow and divide uncontrollably resulting in a mass of tissue which is usually known as a 'tumor'. The symptoms of breast cancer are abnormal lump or swelling in the breast, the most common symptom, the lumps beside the breast or under the arm, unexplained breast pain, abnormal-nipple discharge, changes in breast texture, or changes in the skin on or around the breast [1, 2]

Thus, breast cancer is characterized by the presence of malignant tumors in one of the organ's structures, which arise from the uncontrollable reproduction of cells that have gone through a complex process of disordered transformations and may progress through direct extension or metastatic dissemination [2].

Staging describes how much cancer is present in the patient's body. The size and location of the tumor, as well as the spread the cancer to other parts of the patient's body are the factors, among others, that influence staging a breast cancer. The American Joint Committee on Cancer's TNM classification system is used to stage invasive breast cancer (AJCC) [3].

Accordingly, the basic stages of breast cancer are stage 0, I, II, III and IV and each of them are elaborated as follow.

Breast cancer Stage 0 is defined as the cancer cells are not non-invasive. It is also known as ductal carcinoma in situ. This means there is no evidence of cancer cells or non-cancerous abnormal cells breaking out of the area of the breast where they began, or of getting through to or invading neighboring normal tissue.

Breast cancer stage I refers to an extremely early stage of invasive cancer. Tumor cells have spread to normal surrounding breast tissue but are still contained in a small area at this point.

Breast cancer stage II cancer is defined as cancer that has spread beyond a specific region of the breast. It shows the number of lymph nodes that may contain cancer cells.

Breast cancer stage III breast cancer means that the cancer has spread further into the breast or that the tumor is larger than in earlier stages.

The most advanced stage of breast cancer is stage IV. It has spread to nearby lymph nodes as well as distant areas of the body outside of the breast. This means it could affect the organs, such as your lungs, liver, or brain, as well as your bones [4–7].

The exact causes of breast cancer are largely unknown but demographic change, an unhealthy lifestyle due to economic transition, urbanization, hormonal factors, a family history of breast cancer, and a sedentary lifestyle, among others, played a paramount role in the rising incidence and prevalence of breast cancer in Africa in the last two decades [8–10]. For instance, according to cancer registry reports, breast cancer incidence rised by 3.7% in Uganda and 6.5% in South Africa per year. Moreover, most of the time, African breast cancer patients visit health facilities for treatment only after their breast cancer reached advanced stage. This is mainly due to a lack of awareness about the nature of breast cancer, insufficient screening services, large distances to health facilities, low health seeking behaviour, and poverty [11]. Consequently, treatment was more often palliative than curative [12] and breast cancer is the major cause of mortality and morbidity among women in Africa [8].

The breast cancer burden in Ethiopia was compared with neighboring and peer African countries. The Global Cancer Observatory recent report indicated in 2020 female breast cancer five years prevalence was 48.52 per 100,000 which was Somalia (31.61/100,000) and South Sudan (25.72/100,000) but lower than Eritrea (48.73/100,000), Uganda (55.46/100,000), Sudan (55.62/100,000), Kenya (57.28/100,000), Nigeria (59.31/100,000), Djibouti (74.71/100,000) and South Africa (138.90/100,000) [13].

Breast cancer is the most common and frequently diagnosed disease among women in Ethiopia. According to the GLOBOCAN report, 16,133 women were newly diagnosed with breast cancer in 2020 [14]. The Five-Year National Cancer Control Plan of Ethiopia (2015–2020) indicated a need of US$ 93 million for activities related to cancer prevention, screening, diagnostic, and treatment [15]. The importance of costing has risen over time, mainly because it can help policy makers to develop appropriate health financing policies and strategies for health facilities. A costing study serves as the basis for establishing user fees, evaluating whether health care providers are cost effective, and assessing how resources are used effectively and efficiently [16–18].

This study intended to (a) estimate the total cost of breast cancer treatment for standard breast cancer patients in different stages of the disease, who completed treatment, (b) identify the most important cost drivers, (c) provide evidence on the annual budget needed for full treatment for breast cancer patients at each stage for the next 5 years, and (d) show the economic burden of the disease in Addis Ababa City.

Methods

Study setting

This study was undertaken in the Radiotherapy Center, Tikur Anbessa Specialised Hospital (TASH) in 2018. 84 health professionals (5 oncologists, 41 clinical oncology residents, 1 general practitioner, 3 medical physicists, 2 radiotherapy technicians, 4 pharmacists, 6 radiographers residents), 22 nurses and 6 non-health professional (1 porter, 2 chart keepers, 1 cashier, and 2 secretaries) had been working in the Center, which had a computer tomography (CT) Simulator for diagnosis, a Cobalt 60 for cancer treatment and 18 beds for cancer patients.

Data collection

Primary data using questionnaires were collected from health professionals, who were working in the Radiotherapy Center as well as in other medical and non-medical departments of TASH from July to December 2019. The questionnaires were distributed to 22 respondents, who were selected from pathology, laboratory, pharmacy, surgery, anaesthesiology, oncology, and radiology departments. When the questionnaires were distributed to each respondents, they were asked to read the consent form and sign on it before they start to fill the questionnaire. Thus, all the respondents who filled the questionnaire signed on the consent form. Moreover, the time required to treat a single breast cancer patient was estimated by asking each professional and observing their actual time while they provide health care services.

Secondary data were collected from official reports from TASH, the Ethiopian Ministry of Health and the World Health Organisation. Other quantitative data such as employees salary, cost of pharmaceuticals, construction cost per m^2, Real Gross Domestic Product, foreign exchange rates, governmental total budget, and the government's budget for health and population growth were collected from official reports from TASH departments, the National Bank of Ethiopia, the Ministry of Finance, the International Monetary Fund, and the Central Statistical Agency. The tax revenues that the Ethiopian government will collect during the next five years were forcasted to obtain the total budget to be allocated for health care services.

Prior to extracting data from the patients charts, discussion was made with Oncology department head to anonymized all data to be collected from the charts. Following this, breast cancer treatment data were extracted from 55 selected patients' charts, who were treated between July 2016/17 and June 2018/19. The charts contained full information about the complete treatment given to the patients. For this study, a breast cancer patient was considered to have completed treatment if she took 8 cycles of chemotherapy.

Methods of cost estimation

Costs of breast cancer treatment were calculated at three levels: (a) First, the unit cost of each cost driver and service, (b) the total cost for a single breast cancer patient, and (c) lastly the total cost to treat all breast cancer patients annually (2021–2025), which will be expected to be presented at TASH.

All cost drivers of breast cancer treatment were first identified, and the unit cost of each cost driver was computed using the apportioning method as indicated in Table 1. The salary data were taken from the payroll, which the human resource department of TASH provided. The salaries of human resources were estimated by multiplying hourly salaries and the total time spent to treat each patient. The existing buildings were measured in meter. The unit costs of medical and non-medical furniture and equipment were calculated using cost data from the fixed asset registration book, as well as information from contacted heads of department.

Fixed assets are defined as all types of assets that can provide service for more than one year that includes office and medical furniture, Office and medical equipment, medical and non-medical machines, buildings, land, etc.

The total costs of these items for breast cancer treatment were then calculated by multiplying the unit costs by the number of items utilized and depreciation over time. Depreciation is the value that decrease every time when a fixed asset is used. The cost of each consumable medical item was made available by the Pharmacy of the Radiotherapy center and the main

Table 1. Sources of data and apportioning method for estimating the unit of cost of each cost driver.

Cost driver	Source of information	Units	Apportioning method
Salary of employees	Payroll copy from Human Resource Department	ETB converted to US$	Average monthly salary converted to hourly wage and multiplied by the time estimated for the specific activity
Building	Data collected from construction professionals	Area and ETB converted to US$	Annual depreciation divided by the total number of working hours and multiplied by the amount of time the patient received service
Medical and non-medical furniture and equipment	Data were collected from shops that sold the items	Number of items used	Annual depreciation divided by the total amount of working hours and multiplied by the amount of time the patient received service
Consumable materials and drugs	Pharmacy stores of TASH	Number of items consumed	Based on the dosage determined for the specific treatment
Radiotherapy	Medical physicist unit and patients register in radiotherapy room	Radiation dosis (Gray) given to patients	•The Cobalt 60 radiation source was depreciated for 5½ years and the investment divided by the total doses (Gy) provided to patients during the above-mentioned years •The unit cost of the Cobalt 60 machine was depreciated by 10 years, but since the machine served for more than 10 years, the depreciation value was zero
Overhead costs	The costs of different materials and activities that were used jointly by the Oncology department and other (e.g. utilities, security guard)	ETB converted to US$	10 % of the total of the above costs were taken

ETB: Ethiopian Birr; TASH: Tikur Anbessa Specialized Hospital; US$: United States of America Dollar.

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Table 2. Costed consumable materials.

Service type	Costed consumable materials	Costing method
Consultation	Patient card, pen, prescription papers, and gloves	Unit costs of each materials times number of materials used
Laboratory	Chemicals/reagents for diagnosis	Costs of each type of chemical/ reagents per mg times the quantity of chemical/ reagents used
Pathology	Chemicals, reagents and other related materials for diagnosis	Costs of each type of chemical/ reagents per mg times the quantity of chemical/ reagents used plus the unit costs of each materials times number of materials used
Ultrasound	Ultrasound paper and gel and other related materials for diagnosis	Costs of gel per mg times the quantity of gel used plus the unit costs of each materials times number of materials used
X-ray	Gloves and CD for diagnosis	Unit costs of gloves and CD times number of gloves and CD used
CT-Scan	Gloves, contrast, plastic sheet and other related materials used in the CT scan room for diagnosis	Unit costs of gloves, plastic sheet and other related materials times number of gloves, plastic and other related materials used plus costs of contrast per mg times the quantity of contrast used.
Anesthesia	Chemicals and other related materials for surgery.	Costs of each type of chemical/ reagents per mg times the quantity of chemical/ reagents used plus the unit costs of other related materials times number of other related materials used.
Surgery	Gauze, blades, and other related materials.	Unit costs of gauze, blade and other related materials times number of gauze, blade and other related materials used.
Radiotherapy	The Cobalt 60 radiotherapy source and related materials	Costs per Gray times the quantity of Gray plus the unit costs of other related materials times number of other related materials used.
Chemotherapy	Chemotherapy drugs (e.g. FEC, CMF, and Doxorubicin ACT) and other related materials.	Unit costs of each drug times the quantity of drug plus the unit costs of other related materials times number of other related materials used.

ACT: (Adriamycin)/ Cyclophosphamide (Procytox)/ Paclitaxel (Taxol) CMF: Cyclophosphamide/Methotrexate/ Fluorouracil, FEC -Fluorouracil/Epirubicin/Cyclophosphamide

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pharmacy department of TASH. The total costs of each service was obtained by multiplying the unit costs of each material by the quantity of the materials used. The grand total of all services was found by summing up the total costs of each service. To include the costs of items that are commonly utilized by all departments of TASH, 10% of the total costs of other items were taken as overhead cost.

The types of services that will be provided to breast cancer patients were identified as listed in Table 2. The costs of drugs that were prescribed and subsequently bought by patients, including endocrine treatment (Tamoxifen) were not included, because TASH does not supply these drugs.

The units and total costs of breast cancer treatment were estimated in two scenarios. The first scenario did not include depreciation of fixed assets such as medical and non-medical equipment, machines and furniture, because these items were too old and did not have book value even if they are still giving services. The second scenario includes depreciation by using the depreciation values of the fixed assets based on their current prices, if TASH replaced the existing old fixed assets by new items and renovated the existing old building. Annual depreciation for fixed assets were computed using straight-line depreciation method over different years according to the council of ministers regulation on the federal income tax [19]. Accordingly, computers, software, all medical and non-medical machines and office furniture were

depreciated by 20%, while the Cobalt 60 machine was depreciated by 15%, and building was depreciated by 5% annually. However, depreciation of the source of Cobalt 60 was calculated based on the amount of radiation Gray used and leaked every year.

The medical and non-medical consumable materials were procured between August and October 2019. To estimate the costs of the aforementioned materials in July 2017 and 2019, the costs were discounted by 15 percent due to inflation during these years and converted to US$ using the average exchange rates of the these years. Thus, the treatment costs computed for these patients reflected the costs that TASH incurred during the above-mentioned years.

Following the identification of the types of diagnosis and treatment provided, the costs incurred for breast cancer treatment for a single patient using the prevailing breast cancer treatment practice were estimated.

The new cases of breast cancer were projected based on the growth of the female population per age and the annual growth of incidence rate of breast cancer as per the record of AAPBCR.

The total costs of breast cancer treatment were calculated by multiplying the unit costs of each service by the number of breast cancer patients, who will be treated during the next five years.

These costs were estimated in two scenarios. The first scenario was using the existing fixed assets including building as they are and second scenario was after renovating/replacing the existing building and fixed assets by new ones. These costs were also estimated in three scenarios by assuming the unit costs of inputs will be increased by 10%, 15% and 20%.

It is assumed that TASH will treat all the projected new breast cancer patients using the existing practice and infrastructures. Following these steps, the total costs were estimated in Ethiopian Birr and then changed in US$ using the Wallet Investor website [20].

The economic burden of the projected cost of breast cancer treatment was estimated in terms of the share of the total health budget allocated at a national level, as it is difficult to estimate the health budget in Addis Ababa due to a lack of reliable data. Ethiopia's RGDP for the next five years was forecasted using Autoregressive and Moving Average (ARIMA) and Seasonal Auto Regressive Integrated and Moving Average (SARIMA) models [21, 22].

Ethical consideration

The author obtained ethical approval from the Institutional Review Board of the College of Health Sciences, Addis Ababa University, prior to conducting the study. The study participants provided their consent in writing by signing on the informed consent form attached with the questionnaire.

Results

Costs of breast cancer treatment services for a single patient

A total of 55 breast cancer patients were assessed. Of these, three were stage I, 12 stage II, 29 stage III, eight stage IV and three of an unknown stage. These three patients were categorized as unknown stage because Oncologist did not mention the breast cancer stages in patients' charts. Because of this, these patients were excluded from further considerations. Out of 52 patients, 42 received modified radical mastectomy. When these 42 patients were disaggregated by their stage of breast cancer, 2, 8, 29 and 3 patients were at stage I, II, III and IV respectively. Similarly, among 39 patients to whom radiotherapy was provided and of these 7, 29 and 3 patients were at stage II, III and IV respectively. Chemotherapy was provided to all patients. The chemotherapy and radiotherapy treatments were provided to breast cancer patients in accordance to National Comprehensive Cancer Network Harmonized Guidelines for Sub-

Table 3. Unit cost for treatment by breast cancer stage (April 21, 2020).

Type of service	Cost of treatment per stage in US$ (%)					
	Scenario I excluding fixed assets			Scenario II including fixed assets		
	Stage I	Stage II	Stage III	stage I	Stage II	Stage III
Consultation/ Examination	31 (60%)	31 (4%)	31 (4%)	69 (7%)	69 (6%)	69 (6%)
Laboratory	36 (7%)	36 (5%)	36 (5%)	91 (10%)	91 (8%)	91 (8%)
Pathology	20 (4%)	20 (3%)	20 (3%)	72 (8%)	72 (6%)	72 (6%)
Ultrasound	3 (1%)	3 (0.5%)	3 (0.5%)	13 (1%)	13 (1%)	13 (1%)
X-Ray	2 (0.4%)	2 (0.3%)	2 (0.3%)	14 (2%)	14 (1%)	14 (1%)
CT-Scan		51 (7%)	51 (7%)		55 (5%)	55 (5%)
Surgery	148 (28%)	148 (21%)	148 (21%)	209 (22%)	209 (18%)	209 (18%)
Radiotherapy		118 (17%)	118 (17%)		147 (13%)	147 (13%)
Chemotherapy	297 (55%)	297 (42%)	297 (42%)	488 (51%)	488 (42%)	488 (42%)
Total	**536 (100%)**	**705 (100%)**	**705 (100%)**	**955 (100%)**	**1,157 (100%)**	**1,157 (100%)**

Source: Authors' calculations based on the data collected from respondents

Note: Due to rounding, the sums may not be equal to the total

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Saharan Africa (NCCN) guidelines by prescriping 8 cycles chemotherapy and on average 39 Gray in 13 fractions radiotherapy.

Accordingly, this study found that TASH incurred US$ 33,261 for provision of full treatment for 52 breast cancer patients. When this amount was disaggregated by breast cancer stages, TASH expended US$ 1855, 8221,19558, and 3626 to treat breast cancer patients with breast cancer stage I, II, III and IV respectively. The total costs of breast cancer treatment were again itemized by the type of diagnosis and treatment provided. Accordingly, The cost of chemotherapy, radiotherapy, laboratory and other services was $11211, 7253, 4333 and 10464 respectively.

The cost per patient for each stage was calculated and stage I, II, III and IV were found to cost US$ 618, 735,772 and 584 respectively.

Unit cost of breast cancer treatment by stages and scenarios

Unit cost for treatment by cancer stage is presented by stages and in two scenarios (Table 3). According to scenario I (excluding the values of fixed assets), the treatment costs for breast cancer stage I was US$ 536 whereas for stage II and III the costs of treatment were US$ 705 each. These costs increased to US$ 955 to treat breast cancer stage I and US$ 1157 to treat breast cancer stage II and III each, when the values of fixed assets were included (Table 3). Chemotherapy, surgery, and radiotherapy services took the largest portions of the total cost among the services offered to breast cancer patients, as shown in Table 3.

When the replacement and renovation costs of fixed assets are included (scenario II), the costs of some services were increased while the costs of other services decreased (Table 3).

Cost of treating breast cancer per type of input

In scenario I, consumable materials and human resources took the lion shares of the total cost of breast cancer treatment for all stages using the existing fixed assets. However, if the existing assets are replaced by the new one and the buildings are renovated, the share of each input will vary. With scenario II, the share of consumable materials and human resources was decreased to 38% and 13% for stage I and 39% and 13% for II and III respectively. The costs of medical

Table 4. Cost of breast cancer treatment by type of input (April 21, 2020).

Type of inputs to be used	Treatment cost per type of input and stage of breast cancer in US$ (%)					
	Scenario I excluding fixed assets			Scenario II including fixed assets		
	I	II	III	I	II	III
Consumable materials	360 (67%)	456 (65%)	456 (65%)	360 (38%)	456 (39%)	456 (39%)
Human resource	124 (23%)	150 (21%)	150 (21%)	124 (13%)	150 (13%)	150 (13%)
Medical equipment, machines and furniture	2 (0.5%)	34 (5%)	34 (5%)	101 (11%)	133 (12%)	133 (12%)
Non-medical equipment, machines and furniture	0.3 (0.1%)	0.4 (0.1%)	0.4 (0.1%)	23 (2%)	24 (2%)	24 (2%)
Building	0(0%)	0.2 (0.0%)	0.2 (0.0%)	259 (27%)	288 (25%)	288 (25%)
Others	49 (9%)	64 (9.%)	64 (9%)	87 (9%)	105 (9%)	105 (9%)
Total	**536 (100%)**	**705** (100%)	**705** (100%)	**955** (100%)	**1,157 (100%)**	**1,157 (100%)**

Source: Authors' calculations based on the data collected from respondents.

Note: Due to rounding, the sum may not equal to the total

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equipment, machines and furniture increased to 11% for stage I and 12% to treat stage II and III. The costs of non-medical equipment, machines and furniture increased from 0.1% to 2% to treat stage I, II and III of breast cancer. On the other hand, the construction cost has increased from 0% to 27% for Stage I and 25% for Stage II and III (Table 4).

Comparison of cost of treatment between current practice and NCCN guidelines

Breast cancer treatment costs for one patient at each stage of current Ethiopian practice in TASH and NCCN are similar for nearly all types of services (Table 5). Differences were observed in CT scan diagnosis, which is not prescribed in the current treatment practice while NCCN guideline prescribed it for breast cancer stage I patients. The amount of Gy prescribed in the current radiotherapy treatment practice is a little bit higher than the amount Gy prescribed in NCCN guideline. The total cost of breast cancer treatment with the current

Table 5. Comparison of breast cancer treatment costs between current practice and NCCN guidance (as of April 21, 2020).

Type of service	Cost of BC treatment by stage of breast cancer (US$)							
	As per the current practice				As per NCCN Guidelines			
	Qty	I	II	III	Qty	I	II	III
Consultation/examination	8 visits	31	31	31	8 visits	31	31	31
Laboratory	8 times	36	36	36	8 times	36	36	36
Pathology	1 time	20	20	20	1 time	20	20	20
Ultrasound	1 time	3	3	3	1 time	3	3	3
X-Ray	1 time	2	2	2	1 time	2	2	2
CT-Scan	1 time		51	51	1 time	51	51	51
Surgery	1 time	148	148	148	1 time	148	148	148
Radiotherapy	53.68 Gy		118	118	50 Gy		160	160
Chemotherapy	8 Cycles	297	297	297	8 Cycles	297	297	297
Total		**536**	**705**	**705**		**587**	**747**	**747**

NCCN: National Comprehensive Cancer Network Harmonized Guidelines for Sub-Saharan Africa, Qty: Quantity

Source: Authors' computation based on the data collected from respondents and NCCN guidelines

Note: Due to rounding, the sums may not be equal to the total

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Table 6. Projection of the total costs of breast cancer treatment excluding and including the values of fixed assets from the year 2021 to 2025.

Year	Number of patients	Scenario I excluding fixed assets in thousands			Scenario I including fixed assets in thousands		
		10%	15%	20%	10%	15%	20%
2021	670	540	560	590	870	910	950
2022	700	620	680	740	1,000	1,100	1,190
2023	723	700	800	910	1,140	1,300	1,480
2024	748	800	960	1,113	1,300	1,550	1,840
2025	776	910	1,140	1,410	1,480	1,850	2.290

Source: Authors' computation based on the data collected from AAPCR, CSA and data collected from TASH documents and reports

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treatment practice is US$ 536 to treat a patient in stage I and US$ 705 for stage II and III compared to the total cost of breast cancer treatment per NCCN guideline as US$ 587 for stage I and US$ 747 for breast cancer stage II and III.

Projected costs of breast cancer treatment

The number of new breast cancer patients in Addis Ababa, who might seek treatment in TASH will follow the growth of the female population per age [23] and increase from 670 in 2021 to 776 in 2025 (Table 6).

If the unit costs of materials will increase by 10 percent every year, the total cost of breast cancer treatment for TASH will increase from US$ 540,000 in 2021 to US$ 910,000 in 2025 (Table 6). If the unit costs of materials will increase by 15%, TASH will incur from US$ 560,000 in 2021 to US$ 1.14 million in 2025. However, if the unit costs of medical and non-medical materials increased by 20%, TASH will be forced to incur from US$ 590,000 in 2021 to US$ 1.41 million in 2025.

The estimated costs excluding amortization in scenario I are too low. Thus, the depreciation values of fixed assets were included assuming that the old but functional fixed assets will be either replaced by new one or renovated (scenario II). If the prices of medical and non-medical both resources will increase by 10%, the cost of breast cancer treatment will be increased to US $ 870,000 in 2021 and US$ 1.48 million in 2025 to treat 670 and 776 breast cancer patients respectively. This cost will increase to US$ 910, 000 and US$ 1.85 million in 2021 and 2025 respectively to treat the same number of breast cancer patients. When the prices of both medical and non-medical resources will increase by 20%, the cost of breast cancer treatment will increase to US$ 950, 000 and US$ 2.29 million (Table 6).

Economic burden of breast cancer

The economic burden of the health care service is determined by the share of the total health budget as well as the gross domestic product. Accordingly, if TASH continues to provide treatment, using the existing infrastructure assuming that the costs of inputs will increaseby 10%, 15% and 20%, the share of the costs of breast cancer treatment to the total health budget will be 0.042%, 0.043% and 0.045% in 2021 respectively. These shares will be increased to 0.065%, 0.081% and 0.1% in 2025. If TASH replaces the old medical and non-medical machines, equipment and furniture by new one and the existing building is renovated and if the costs of inputs increased by 10, 15 and 20%, the share of the breast cancer to the total health budget will be 0.067, 0.070 and 0.073% in 2021 respectively and these shares will be increased to 0.105, 0.131 and 0.162% in 2025.

Discussion

This study found considerable differences of costs for optimal treatment regimen of breast cancer patients. Chemotherapy was the most expensive, followed by radiotherapy and consultation costs. This study found that according to the current treatment practices at TASH, the total costs of breast cancer treatment significantly increased with higher stages of disease. Patients with stage two and three disease needed more expensive treatment compared to stage one. Out of the total cost incurred to optimally treat 55 breast cancer patients, 6% were spent for treatment of patients with stage I, 26% for stage II and 61% of the total cost for stage III breast cancer patients. Costs for all new breast cancer patients, who will present at TASH for treatment during the next five years were projected [24].

Guzha et al. also found somewhat similar findings that of the total cost of breast cancer treatment 6%, 47% and 35% of costs were incurred for treating stage I, II and III cancer respectively, though these costs were paid by the patients [25]. However, Nguyen et al indicated in their study that the initial treatment cost of breast cancer treatment was only US$ 128.7 for stage I but US$ 684.1 for stage III; for stage IV the treatment cost decreased to US$ 537.9. The five year total treatment cost increased from US$ 568.6 for stage I to US$ 901.8 for stage II but for stage III and IV the treatment cost decreased to US$ 816.1 and US$ 603.4 respectively. The reason for this decline was that the follow-up treatment for breast cancer in the years after the initial treatment was relatively simple [26]. Certainly the costs per patient increased with higher stages seeing the majority of patients treated for advanced stage further increased the costs. Furthermore, this study found that TASH incurred US$ 11,704 for chemotherapy which was US$ 180.66 per patient. Those studies, which were conducted at TASH, Addis Ababa, Ethiopia and Groote Schuur Hospital, Cape Town, South Africa, indicated that patients incurred far higher costs on average US$ 1,188 and US$ 1,489 for chemotherapy respectively [25]. A study conducted in Moroco on Unit price for different drugs, cost of protocols by cycle and cost of individual whole treatment, the unit cost of chemotherapy drugs for example Cyclophosphamide (1000 mg) was US$ 7.28. The total cost of chemotherapy treatment was also US$ 84.50 for AC, US$ 1105 for Docetaxel and US$ 1560 for Trastuzumab [27]. In Vietnam the average cost of chemotherapy treatment was US$ 476.48 [26]. This shows that chemotherapy costs were rather low in Addis Ababa compared to other settings were more modern substances are used.

Consumable materials took a high share out of the total costs of breast cancer treatment in all scenarios. If maintenance costs were included such as renovation of existing buildings, the share of the cost for building-renovation would be higher than the share of cost of human resources. In terms of costs of utilized for consummable inputs, the advanced stages were more costly than earlier stages of breast cancer. The costs of breast cancer treatment according to the NCCN guideline for SSA was slightly higher than the costs of breast cancer treatment according to current practice due to differences in imaging utilization and low-cost radiotherapy.

Total costs certainly depend on numbers of patients in need for therapy. The projection of the number of new breast cancer cases based on AAPBCR and CSA data indicated an increase. This projection might even be an underestimate, because with expected higher awareness, the number of Addis Ababa residents, who demand breast cancer treatment may increase. As the number of breast cancer patients will increase from year to year, the budget to be allocated would need to rise to US$ 1.5 million in 2025. This is due to the increase of investment costs for newly procured medical and non-medical equipment and furniture, as well as the cost of renovation of the existing building (increase on average by 144%). Because of this, the estimated and projected total cost of breast cancer treatment will be 1.02% and 1.251% of the total

health budget in 2021 and 2025 respectively. This will compel TASH to mobilise resources from both domestic and foreign sources. High costs for breast cancer treatment are also reported from other countries. Saber Boutayeb et al. also revealed that the cost of chemotherapy treatment for a breast cancer patient varies between US$ 507 up to US$ 30,088. In Vietnam also, the initial treatment and 5-Year total cost for treatment course was US$ 632.86 and US$ 975.01 respectvely [26]. The government of Moroco was suggested to allocate annual between US$ 13.3 million and US$ 28.6 million for breast cancer treatment [27]. These studies show that understanding the total cost of breast cancer treatment is critical, as it will inform the decision-makers on financing breast cancer treatment.

In summary, this study found that the budget required to provide breast cancer treatment for new patients depends on the number of new patients, the proportion of advanced stage as well as the detailed decision on costly targeted therapy such as trastuzumab. It should be noted that, promoting of earlier treatment of breast cancer should be given high priority to considerably reduce the economic burden of breast cancer treatment as well as increasing survival rates [28, 29].

Thus, the Ministry of Finance and Ministry of Health of Ethiopia and TASH are advised to use the data and findings of this study as a baseline, while planning and budgeting for breast cancer prevention and treatment.

Moreover, from a public health perspective, the reported data in this study can be used as a resource to develop ideas on budgeting for the different components of breast cancer therapy.

Limitation of the study

The study has the following limitations: First, the study focused on the treatment given at TASH only. TASH is the most comprehensive cancer center in the country and sets high standard. We purposely choose a guideline concordant approach to assure the maximum benefit to the patients. Second, the study did not include the costs incurred to treat breast cancer stage IV, costs of treatment for adverse effects of medication given to breast cancer patients, and costs for breast cancer inpatient treatment. This would add additional costs but can have very high variability due to personal preferences and individualized approaches. Third, additional factors such as inflation, pandemic or difficulties of procurement may also alter prices of items.

Conclusion

This study shows the magnitude of current costs for breast cancer service in Addis Ababa, Ethiopia. In detail, main drivers are advanced stage, investment costs such as radiotherapy machine as well as the increasing total number of patients in need of care. Hence, to alleviate the economic burden of breast cancer treatment, promoting of early diagnosis is vital. Nevertheless, it should be noted that as women's awareness about the benefits of breast cancer treatment increase, the demand for innovative breast cancer treatment would rise as well. Negotiations with pharmaceutical companies could possibly provide access to modern therapy for low-resource countries. In general, innovative financing mechanisms have to be found to meet the demand for cancer care. Hence, we recommend that international partnership should be sought to assure costly investments, policies should be carefully revised and social and community based health insurances should include breast cancer in their schemes.

Supporting information

S1 File. Estimted cost of breast cancer treatment at TASH.
(XLSX)

S2 File. Unit costs of breast cancer treatment.
(XLSX)

S3 File. Comparison of the cost of BC treatment.
(XLSX)

S4 File. Projected BC treatment cost.
(XLSX)

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Erklärungen

(1) Ich erkläre, dass ich mich an keiner anderen Hochschule einem Promotionsverfahren unterzogen bzw. eine Promotion begonnen habe.

(2) Ich erkläre, die Angaben wahrheitsgemäß gemacht und die wissenschaftliche Arbeit an keiner anderen wissenschaftlichen Einrichtung zur Erlangung eines akademischen Grades eingereicht zu haben.

(3) Ich erkläre an Eides statt, dass ich die Arbeit selbstständig und ohne fremde Hilfe verfasst habe. Alle Regeln der guten wissenschaftlichen Praxis wurden eingehalten; es wurden keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt und die den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht.

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Date and Signature