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Krebs bei Frauen in Afrika
Female Cancer in Africa

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2. Review (including bibliography)

Female cancer is a major cause of suffering and death in low- and middle-income countries such as Ethiopia. Within our university collaboration partnering with Addis Ababa University, several projects assessed breast and cervical cancer patients´ presentation, therapy, tumour biology, and outcome in rural and urban Ethiopia. One large retrospective hospital-based cohort including more than 1000 breast cancer patients in Addis Ababa and one hospital-based prospective cohort of 107 breast cancer patients in Aira, rural Ethiopia, were assembled. All patients received surgery, whereas adjuvant therapy was available in Addis Ababa only. Hormone-receptor status was analysed in both cohorts. More than 1000 cervical cancer patients were included at the only radiotherapy center of the country, Addis Ababa.

Breast cancer patients presented at young age and with advanced stages similar to other African settings with young population structure and low awareness. Survival was worst in the rural setting with surgery only; none of the patients were able to travel to the capital for additional treatment. Surprisingly, both breast cancer cohorts showed two thirds endocrine responsive tumours different to most results from West Africa, indicating genetic differences in geographic regions of Africa. Cervical cancer patients presented similarly young and with advanced disease in this setting without any screening program. Patients who received higher doses of radiotherapy from the only Cobalt machine in the country showed considerable survival benefits in a dose-dependent manner comparing to those patients who discontinued their schedule earlier.

Improving cancer care in Ethiopia needs a comprehensive system-wide approach. Cancer awareness among the population is crucial to downstage breast cancer. Screening needs to be implemented to reduce the burden of cervical cancer in Ethiopia. Treatment options are available in the capital city, but capacity is low, especially concerning radiation therapy. De-centralization of oncology units is thus urgently needed to reduce huge disparities in regional care. Endocrine therapy seems a cheap and feasible option to expand basic oncologic care to the rural setting of a general hospital until more cancer centers are available as planned by the National Cancer Control Plan. Based on our results, we have focussed on the underserved rural setting. We implemented and evaluated a Tamoxifen donation programme in eight hospitals, and we started a population-based cervical cancer screening programme to optimize screening modalities.

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2. Referat (mit bibliographische Beschreibung)

Krebs bei Frauen ist auch in Ländern mit niedrigem Einkommen wie Äthiopien eine wesentliche Ursache für Leiden und Tod. Im Rahmen unserer Kooperationspartnerschaft mit der Universität Addis Abeba untersuchten wir Charakteristika, Therapie, Tumorbiologie und Krankheitsverläufe von Brust- und Gebärmutterhalskrebs-Patientinnen in Äthiopien. Eine große retrospektive Krankenhauskohorte mit mehr als 1000 Brustkrebspatientinnen aus Addis Abeba und eine prospektive Kohorte von 107 Brustkrebspatientinnen aus dem ländlichen Aira wurden zusammengestellt. Alle Patienten wurden operiert, die adjuvante Therapie gab es nur in Addis Abeba. In beiden Kohorten wurde der Hormonrezeptorstatus analysiert. Mehr als 1000 Patientinnen mit Gebärmutterhalskrebs wurden aus dem einzigen Strahlentherapiezentrum in Addis Abeba zusammengestellt. Brustkrebspatientinnen stellten sich in jungem Alter und in fortgeschrittenem Stadium vor, ähnlich wie in anderen afrikanischen Ländern mit junger Bevölkerungsstruktur. Die Überlebenswahrscheinlichkeit von ländlichen Patientinnen war am geringsten. Diese konnten für eine zusätzliche Behandlung nicht in die Hauptstadt reisen. Überraschenderweise waren zwei Drittel der Tumore beider Brustkrebs-Kohorten Hormonrezeptor-positiv. Das unterscheidet sich von Ergebnissen aus Westafrika, was auf einen genetischen Unterschied hindeutet. Gebärmutterhalskrebs-Patientinnen stellten sich – ohne Screening-Programm – ähnlich jung und mit fortgeschrittener Erkrankung vor. Patientinnen, die eine adäquate Strahlentherapie-Dosis durch das einzige Cobalt 60-Strahlentherapie-Gerät des Landes erhielten, zeigten im Vergleich zu den Patientinnen mit Abbruch der Behandlung dosisabhängig erhebliche Überlebensvorteile. Wir folgern, dass die Verbesserung der Versorgung von Krebspatientinnen in Äthiopien einen systemweiten Ansatz erfordert. Das Bewusstsein in der Bevölkerung ist für die Früherkennung entscheidend. Screening und Impfung könnten Gebärmutterhalskrebs langfristig reduzieren. In der Hauptstadt stehen Behandlungsmöglichkeiten zur Verfügung, die Kapazität besondere der Strahlentherapie ist jedoch gering. Eine Dezentralisierung der Onkologie-Zentren ist erforderlich, um die großen Ungleichheiten in der Versorgung abzubauen. Die endokrine Therapie ist eine kostengünstige und praktikable Option, um die Versorgung in ländlichen Allgemeinkrankenhäusern zu verlagern, bis mehr Krebszentren zur Verfügung stehen, wie im National Cancer Control Plan vorgesehen. Basierend auf unseren Ergebnissen haben wir ein Tamoxifen-Spendenprogramm in acht ländlichen Krankenhäusern implementiert und evaluiert, sowie ein bevölkerungsbezogenes Screening-Programm für Gebärmutterhalskrebs begonnen.

Kantelhardt, Eva Johanna: Krebs bei Frauen in Afrika, Halle (Saale),
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4. List of abbreviations and symbols

95% CIs – 95% confidence intervals

AIDs – acquired immune deficiency syndrome

BRCA1 – breast cancer 1

C – clinical

FIGO – International Federation of Gynecology and Obstetrics

FNAC – fine needle aspiration cytology

HIV – human immunodeficiency virus

HPV – human papilloma virus

HR – hazard ratio

LoE – level of evidence

M – metastasis

N – nodal status

PR – prevalence ratio

T – tumour size

5. Habilitation

1 Introduction

1.1 Chronic diseases in low and middle income countries

Communicable diseases, malnutrition, and maternal morbidity and mortality still present as large global health problems. At the same time, the epidemiological shift towards an increasing burden of non-communicable diseases is becoming apparent in many low and middle income countries. Cardiovascular and chronic pulmonary diseases, cancer, and diabetes account for the majority (60%) of deaths in the world, with 80% of these in low and middle income countries [Marrero 2012]. More than 20% of these deaths from non-communicable diseases are cancer deaths [WHO 2015]. This disease burden additionally strikes low and middle income countries' health systems, which are already struggling to offer adequate care for the most pressing communicable diseases and maternal and child health care. Starting 2011, the high-level meeting of the United Nations has focused attention on non-communicable diseases (chronic pulmonary, cardio-vascular, diabetes, and cancer) [United Nations 2012]. This has encouraged clinicians and researchers in various countries to improve activities and publish evidence available on non-communicable diseases.

1.2 Female cancer in sub-Saharan Africa

In sub-Saharan Africa, women acquire about 370,000 new cases of cancer every year, of which two-thirds are breast and cervical cancer. From the latter, 63,100 and 57,200 women will die each year, respectively [Parkin 2014]. This combined number of deaths is now approaching the number of maternal deaths in the region (179,000 in 2013) [WHO 2013]. The majority of these women are below the age of 50. Thus, female cancers are likely to hit families equally hard as premature deaths due to maternal causes or HIV – and cancer should equally receive due attention in sub-Saharan Africa [Denny 2017; Ginsburg 2017].

Breast cancer incidence in Africa is generally rather low compared to data from Europe and the US. Most of the registries report incidence rates of less than 30/100,000 in females. The highest incidence is reported for North Africa. In addition to the island populations of Mauritius and Reunion, the highest rates are seen in Kenia and in Zimbabwe (Harare and Bulawayo). The lowest recorded incidence rates are in the rural populations of Gambia [Parkin 2018] – see figure 1.

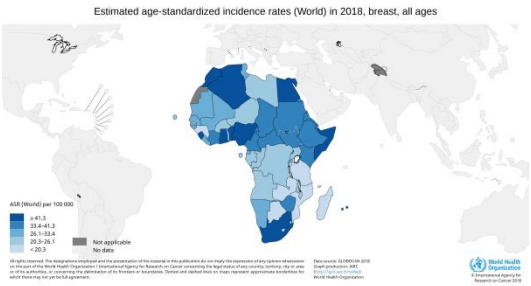

Figure 1: Breast cancer incidence rates in Africa (taken from Globocan 15.4.2017 [Ferlay 2018])

There have been rapid **changes over time** in the incidence of breast cancer in sub-Saharan Africa. Rates of increase in the last 20 years were 3.6% per year in Kampala (Uganda) [Wabinga 2013] and 4.9% per year in the population of Harare (Zimbabwe) [Chokunonga 2013]. In South Africa a recent publication from a rural registry showed an annual increase of 4.3% since 1998 [Somdyala 2015]. These changes are most likely – apart from better cancer reporting – associated with declining fertility in successive generations of African women [Corbex 2014], and changing lifestyles with respect to, for example, increasing overweight/obesity, declining levels of physical activity, reduced duration of breast feeding, and, possibly, increasing alcohol consumption.

The **young age** structure of African populations means that in hospital case series the average age at diagnosis in Africa is lower than in populations in North America and Europe. This early age at diagnosis is often mentioned in breast cancer reports from Africa, but has no etiological significance since age-specific rates are similar [Corbex 2014]. A direct comparison between black and white females in the USA only shows a slightly higher incidence of breast cancer in black females at young ages (<45 years) [Howlader 2014; Newman 2014].

In Africa, **tumour stage** at presentation is generally advanced as a recent meta-analysis by Jedy-Agba and colleagues has shown [Jedy-Agba 2016]. Association of tumour stage and distance to health service has also been reported [Dickens 2014]. Since the majority of those advanced T3 tumours will already have developed metastases at the time of diagnosis, survival time is expected to be short. Follow-up studies of unselected patients diagnosed with breast cancer in 1993–97 have been completed in Harare (Zimbabwe) and Kampala (Uganda) [Gondos 2004; Gondos 2005]. In Harare, five-year **survival** in black African females was 38%, compared to 74% in Caucasian females of the same city, and 45% in Kampala. The CONCORD 2 study analysed data from 279 population-based cancer registries. Striking differences in outcome are seen: high income countries showed survival rates of 85% and more compared to, for example, 53% in South Africa (most reliable data from Africa) [Allemani 2015]. In the USA, there are extensive data on breast-cancer survival showing excellent outcome. When looking at black females in the USA, there is only a weak trend to diagnosis at later-stage disease and poorer survival even within the same stage groups [Dignam 2000]. This suggests that the unfavourable outcome in Africa is mostly due to late stage at diagnosis and that unique tumour biology in women of African descent plays some role.

Differences in the **biology** of breast carcinomas between black and white females have indeed been reported. Tumours in black Americans are slightly more likely to be of higher grade and

Estrogen-receptor negative than observed among white Americans [Jemal 2012]. Up to now there are only hospital case series describing pathologic features of African breast cancer patients. Aggressive clinical features such as triple negative and inflammatory disease have frequently been documented in clinical series from Africa. A reason is probably that relative proportions are high because of lower incidence of other forms [Corbex 2014]. Case series from several centers in Africa have reported that hormone receptor negative cases are predominant. However, in a recent meta-analysis, Eng *et al.* found that generally there is great heterogeneity concerning proportions of Estrogen receptor-negative disease among African publications. Assuming a better specimen quality in prospectively collected specimens, the proportions for Estrogen receptor-positive disease were more than half 0.59 (0.56-0.62) and triple negative tumours only 0.21 (0.17-0.25), respectively. However, they noted the low methodological quality of many studies in terms of the representativeness of their case series and the quality of the procedures for collection, fixation, and receptor testing, which undoubtedly influenced many of the results [Eng 2014].

There are many studies showing various factors increasing the risk for diagnosis of breast cancer. The majority of the data is derived from European and US population. Some data from Africa is available. The most important risk factor is **age**. According to United Nations population estimates, the population of Africa between 2010 and 2030 is projected to increase from 1.03 billion to 1.63 billion. Those 60 years and older, the ages at which cancer is most frequently diagnosed, will increase from 55 million to 103 million. **Family history** has been shown to be a marker of breast cancer risk in the African setting [Okobia 2006]. Part of this risk is mediated by the major susceptibility genes BRCA1 and BRCA2 (about 2% of breast-cancer cases in Europe), but although several distinct mutations in these genes have been identified in black people in the USA, very little is known of the prevalence of these mutations in African populations [Fackenthal 2012]. Due to the great genetic diversity throughout the continent [Gomez 2014] evidence will remain limited until genetic testing is easily accessible. A genome-wide association study in women of African ancestry in the USA has suggested the possibility of some distinctive common variants associated with breast cancer as compared with European populations [Oluwagbemiga 2012].

Breast-cancer risk is also related to reproductive factors, body-mass index, high alcohol consumption, low physical exercise levels, and exposure to exogenous hormones such as contraceptives or postmenopausal hormone replacement therapy. A review by Brinton *et al.* (2014) provides a useful summary of knowledge concerning the role of these risk factors on breast cancer risk in sub-Saharan Africa. The authors speculate also on the possible role of microbiomes, compromised immune states (due to infections, or exposure to chemicals such as insecticides),

environmental Estrogens, and the widespread use of skin lighteners and hair relaxers by African women [Brinton 2014].

To the health care providers, a **different breast cancer disease** is seen in Africa compared to developed countries: there is low awareness and very little general screening activities such as clinical breast examination. Women with risk factors are not aware, and there are no options to utilize mammography, ultrasound, or MRI devices to screen high risk groups. Breast cancer patients are predominantly young with advanced stage tumours. The provision of **treatment** in a low resource setting is difficult and there are great challenges concerning distance to central oncology centers, availability of chemotherapy, stock-keeping, safe administration, and others. Other open questions are how to de-centralize palliative care [Cardoso 2013], how to optimize neo-adjuvant treatment, how to up-scale the use of endocrine treatment, and how to best utilize scarce radiotherapy facilities [Kantelhardt 2015]. Several organizations such as the Breast Health Global Initiative – now BCI2.5 – and the National Cancer Control network have developed and published resource-stratified guidelines to take this situation into account [Anderson 2014; National Comprehensive Cancer Network 2018; Gradishar 2017]. There is an urgent need to find acceptable strategies to improve the outcome of this most common female cancer in less-resourced settings [Denny 2017].

Cervical cancer is still very wide spread in Africa. In many countries it is the number one cancer of all. High-risk human papilloma virus (HPV) is the known causative agent of the disease. The majority of women acquire HPV with the uptake of sexual activity. Also important for Africa, non-sexual transmission, e.g. in crowded housing, is reported [Sabeena 2017; Liu 2016]. After some months or years the virus is cleared and no longer detectable. Only few women have persistent infection with consecutive dysplasia and eventually invasive cancer [Bosch 2002]. There are risk factors for incidence and progression of HPV infection such as chlamydia trachomatis, herpes simplex, and HIV [Denny 2012b]. Regions of Africa with high HIV prevalence also have a high incidence of cervical cancer [Chirenje 2005]. Trends over time show increasing incidence rates especially in East Africa and Southern Africa [Chokunonga 2013]. Due to lack of prevention service and concomitant HIV/AIDS epidemic a continuous rise is expected over the next 20 years [Vuyst 2013].

Types of **HPV** were analysed in 59 countries showing HPV 16 and 18 among the top-10 high-risk types in the general healthy female population. Studies from sub-Saharan Africa showed the highest prevalence of HPV in normal population (24%) [Bruni 2010]. **Vaccination** is an effective

option for prevention. It is important to develop a delivery model and select the target population and community. Vaccination needs sensitization, recruitment and consent strategies, human resources, logistics, and supply chain management. Up to now Rwanda Is the only country in sub-Saharan Africa which successfully introduced HPV vaccination for all eligible girls. School vaccination programmes have been shown an effective strategy of delivery in the country [Torres-Rueda 2016]. Other countries are in the process of establishing cool-chain capacities and developing a vaccination strategy via demonstration projects [GAVI Ethiopia 2018].

The majority of Western countries have reduced the burden of cervical cancer by introducing pathology-based **screening** programmes to detect treatable pre-invasive lesion [Vaccarella 2013]. Visual inspection of the cervix with acetic acid and cryotherapy is a low-tech, cost-effective method recommended for low-resource settings. Recently also HPV-testing and cryotherapy have been suggested as more sensitive methods in low resource settings. Introduction of such screening procedures will eventually decrease the number of cervical cancer cases in a cost-effective way [Denny 2015].

Currently still many women eventually present with advanced cervical cancer to a central oncology centre in the African setting. Primary **treatment of cervical cancer** according to staging consists of either surgery or a combination of radiotherapy and chemotherapy. The common staging system for cervical cancer has been defined by the "International Federation of Gynecology and Obstetrics" (FIGO). Manual examination by an experienced physician will assess the tumour size and relationship to neighbouring organs [Pecorelli 2009]. Early cervical cancer (stages of FIGO IA1, IA2, IB1, IIA1) is an indication for radical hysterectomy, while stages of FIGO IIB and higher and FIGO IB2 and IIA2 with risk factors are treated with primary concurrent radiochemotherapy [AWMF 2014]. Surgical service for cancer is still limited in Africa and in Ethiopia [Dare 2015]. Low numbers of operable early cases due to lack of awareness, delay in health care provision, and waiting times, few experienced surgeons and lack of facilities are common scenarios. Later stages are treated by radiotherapy and concomitant chemotherapy if available. However, only 23 of 52 African countries are known to have radiotherapy with 140 machines covering 34% of the need [Abdel-Wahab 2013; Zubizarreta 2017].

In summary high incidence rates of cervical cancer are still seen in Africa. This is mainly due to the absence of effective vaccination and screening programmes. The common high-risk HPV types 16 and 18 can also be found and are common especially in the HIV positive population. Lack of awareness leads to late presentation and allows only palliative therapy.

For example, radiotherapy (with or without chemotherapy depending on availability) is the main form of treatment in the oncology center in Addis Ababa, Ethiopia.

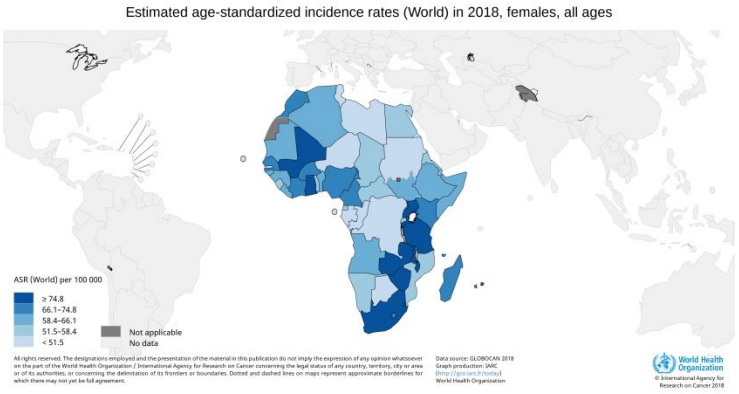

Figure 2: Cervical cancer incidence rates in Africa [taken from Cancer Today [Ferlay 2018]]

1.3 Female cancer control in sub-Saharan Africa and Ethiopia

As mentioned before, cancer is an increasing problem in Africa because of population aging and growth, increased prevalence of risk factors associated with economic transition (including smoking, alcohol intake, obesity, physical inactivity, and reproductive behaviour), and certain infectious agents of importance in cancer aetiology up to 33% [Parkin 2014; Torre 2017]. From a population perspective, female cancer is a rare event seeing incidence rates of, for example, 141 per 100,000 person years in Ethiopia. Nevertheless, since female cancer is a chronic condition with a long illness period before death affecting adult women (often responsible for the whole family), it has a high impact on the health system and the society. Recently, following "African first ladies against AIDS", the "African first ladies initiative to fight against women´s cancers" led by Princess Nikky of Nigeria has gained visibility and public awareness [Oluwole 2013]. Large project funding has been made available through the "Pink Ribbon Red Ribbon" initiative (http://pinkribbonredribbon.org/). There is a need for a systematic cancer control programme to maximize the effects of scarce resources. Effective control programmes require adequate information on the size, nature and evolution of the health problems. Population-based cancer registry data are essential components in the planning and monitoring. In Africa, the data are particularly important, as there are no accurate mortality statistics on cancer available from civil registration systems on the continental mainland [Bray 2015b; Islami 2017].

Evidence-based strategies to reduce cancer mortality are well known from Northern countries, but the approaches need to be adapted to sub-Saharan Africa. Some countries have outlined national cancer control programmes and guidelines [Stefan 2013], but implementation is insufficient, partly due to resource constraints.

Problems seen on the pathway to care are multifaceted and complex (figure 3). Breast cancer health care clearly needs early diagnosis and treatment as main pillars. There are attempts to increase diagnostic and pathology service, adapt treatment guidelines, and provide decentralised access to adjuvant and palliative care [Vanderpuye 2017]. The vaccination and adapted secondary prevention approaches for cervical cancer are still reaching too few women in sub-Saharan Africa. In case of symptoms, first contact might be a traditional healer instead of a primary health care worker. Still, even if care is sought at the primary care level, providers often do not have sufficient skills and knowledge, and the primary care structures are not prepared to deal with chronic diseases. Mid-level hospitals provide some surgery – often without access to quality pathology – but are unable to provide oncologic therapy. Patients will only reach the tertiary facilities offering cancer care in an advanced stage of the disease. Follow-up of cancer patients is nearly non-existent. Clearly, patient pathways are usually not smooth and discontinuation is common. The challenges for a better system are at all levels, especially when referral and collaboration is needed. Up to now there is strong focus on cervical cancer screening and pilot HPV vaccination; up scaling clinical treatment options is still a gap to be filled.

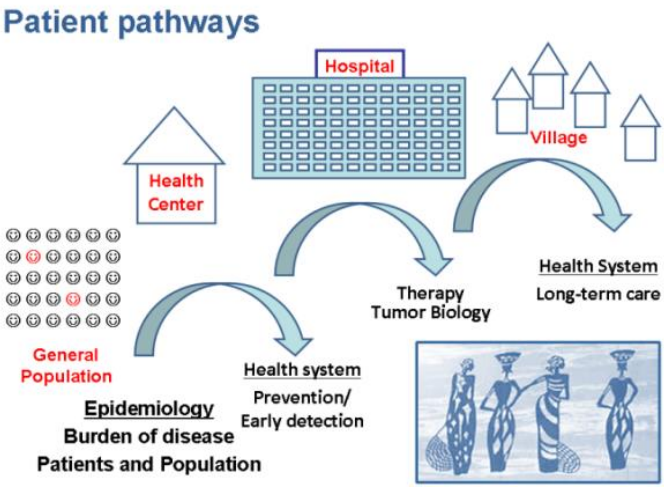

Figure 3: Pathways to care for oncologic patients

The main goal of this research was therefore to obtain evidence on clinical care for female cancer patients in sub-Saharan Africa and especially Ethiopia. The focus is on breast and cervical cancer since these proved to be the number one female cancers on the continent. The long-term question is how to offer integrated health services for female cancer in Africa.

1.4 Collaboration with Ethiopia

Since 2009 there is a lively university partnership between Martin-Luther-University Halle, Germany, and **Addis Ababa University, Ethiopia**. Like most low-income countries, Ethiopia (99 million inhabitants) has only 0.7 health workers per 100,000 population (recommendation by WHO is at least 2.3). There are well established nation-wide health-extension workers (one year education, 2 workers per 8000 population) and nurses/health officers at health centers. Above all, the rural population is largely underserved concerning physicians; there is only one family doctor per 47,000 people, a small number even for sub-Saharan Africa. The life expectancy is 57 and 60 years (m/f); general problems are water supply, nutrition, and education. The HIV rate is only 2.4% nationwide [CSA Ethiopia 2012].

In addition to the great successes in the reduction of infectious diseases, mother-child health and malnutrition, chronic diseases are now becoming a problem. Since two years, the Ministry of Health has increasingly looked into cancer care. There is a first **National Cancer Control Plan**. The annual conference of the “African first ladies' fight cervical, breast and prostate cancer" initiative was held in Addis Ababa in 2016. H.E. Roman Tasfaye, the Ethiopian Prime Minister participated in the program. Surely the recent appointment of the former Ethiopian Minister of Health, H.E. Dr. Tedros Adhanom Ghebreyesus, as Director General of the WHO will enhance the fight against cancer in Ethiopia. The oncological care of the population is currently provided almost exclusively by the Addia Ababa University Oncology Center. It is currently the only source of radiation therapy in the country. The government has been planning decentralization, training, and construction measures. Investments have partially been carried out, but there is still no other location providing radiotherapy. Since 2015, there has been a National “Cancer Control Plan” and a “Guideline for Cervical Cancer Prevention and Control”. First pilot projects for HPV vaccination were implemented. For five years there have been experiences with cervical carcinoma screening by “visual inspection with acetic acid and cryotherapy” in HIV patients in Addis Ababa (15,000 women screened). A national plan now aims at countrywide coverage. The government has already made investments in cryotherapy machines. For breast cancer, availability of chemotherapy has been improved, more oncologists are trained, and decentralized treatment is planned.

2 Objectives

The **overall objective** of the research activities within the collaboration between Addis Ababa University, Ethiopia, and Martin-Luther-University Halle, Germany, was to jointly generate evidence on clinical female cancer care as defined by information on diagnosis and treatment of breast and cervical cancer in Ethiopia in the context of sub-Saharan Africa. This thesis will present and discuss results of a literature review on breast cancer in Africa [Kantelhardt 2015], two hospital cohort studies on characteristics, therapy, and outcome of breast cancer patients [Kantelhardt 2014a; Eber-Schulz 2018] and results of a hospital cohort study on cervical cancer patients [Kantelhardt 2014b and Moelle 2018] in Ethiopia as well as a study on immunohistochemistry features of breast cancer in Ethiopia [Kantelhardt 2014c].

This habilitation is based on the following publications

Kantelhardt EJ.; Zerche, P.; Mathewos, A.; Trocchi, P.; Addissie, A.; Aynalem, A. *et al.* (**2014a**): Breast cancer survival in Ethiopia: a cohort study of 1,070 women. In: *International Journal of Cancer* 135 (3), S. 702–709. DOI: 10.1002/ijc.28691.

Kantelhardt EJ; Moelle, Ulrike; Begoihn, Matthias; Addissie, Adamu; Trocchi, Pietro; Yonas, Bekuretsion *et al.* (**2014b**): Cervical cancer in Ethiopia: survival of 1,059 patients who received oncologic therapy. In: *Oncologist* 19 (7), S. 727–734. DOI: 10.1634/theoncologist.2013-0326.

Kantelhardt EJ; Mathewos, Assefa; Aynalem, Abreha; Wondemagegnehu, Tigeneh; Jemal, Ahmedin; Vetter, Martina *et al.* (**2014c**): The prevalence of Estrogen receptor-negative breast cancer in Ethiopia. In: *BMC Cancer* 14, S. 895. DOI: 10.1186/1471-2407-14-895.

Kantelhardt EJ; Muluken G; Wondimu A; Sefonias G; Gebert C; Unverzagt S; Addissie A (**2015**): A systematic review on breast cancer therapy and outcome in Africa. In: Breast Care (Basel) 10 (6), S. 364-370. DOI: 10.1159/000443156.

Eber-Schulz P; Tariku W; Reibold C; Addissie A; Wickenhauser C; Fathke C; Hauptmann S; Jemal A; Thomssen C; **Kantelhardt EJ** (**2018**): Survival of breast cancer patients in rural Ethiopia. In: *Breast cancer research and treatment*. (170) 111-118. DOI: 10.1007/s10549-018-4724-z.

3 Material and methods

3.1 Systematic review on breast and cervical cancer

First we compiled a systematic review on breast and cervical cancer care in Africa to assess existing evidence. The search was performed to identify publications related to studies describing female cancer (breast and cervix) and Africa. All publications were screened by title, keywords, abstract, and full texts for relevant publications. Inclusion criteria were all studies describing treatment and/or outcomes of breast and cervical cancer in Africa. Exclusion criteria were cross-sectional studies without information on therapy, studies on screening methodology, studies on pathologic material, studies on African Americans only and studies conducted on non-African patients. We screened all major online databases such as MEDLINE (Ovid), CENTRAL, African Journals Online (AJOL), African Index Medicus, The Breast Health Global Initiative, POPLINE, and SurvCan. Additionally, we performed a search in MEDLINE (PubMed) for relevant topics, such as burden, awareness, risk factors, tumour biology, and healthcare services (PubMed search for 'Breast/cervix uteri neoplasm AND Africa'). Relevant articles from the last five years and selected articles from before were presented as a brief overview. The review on breast cancer was published in 2015 [Kantelhardt 2015]. The publications found on cervical cancer were used to interpret the results of the hospital cohort study.

3.2 Hospital based cohorts of patients with breast and cervical cancer

To describe patients, presentation, tumour characteristics, treatment, and outcome, hospital cohorts of breast and cervical cancer patients from Addis Ababa were studied. Collaboration with the only oncology center in Ethiopia gave the unique chance to retrospectively assess large patient cohorts. A retrospective five-year cohort of breast cancer patients [Kantelhardt 2014a] and a four-year cohort of cervical cancer patients [Kantelhardt 2014b] were assembled at Addis Ababa University Hospital. More than 1000 patients each were collected and followed. To additionally describe breast cancer patients in the rural setting, we set up a prospective hospital cohort in the remote rural Aira hospital since 2010. Aira hospital is a faith-based hospital serving a population of about 500,000. On average, 20 breast cancer surgeries were performed annually [Eber-Schulz 2018].

Ethical approvals had been obtained from Addis Ababa University Medical Faculty Ethical Review Board and also Martin-Luther-University Ethical Review Board. Due to the retrospective nature of the study and analysis using pooled, anonymous data, no individual informed consent has been obtained, except for the rural breast cancer cohort that involved tissue collection.

For the **urban breast cancer cohort**, women with a histologically verified primary diagnosis of invasive carcinoma of the breast (International Classification of Disease-Oncology (ICD-O-3) codes C50.0-9) without evidence of distant metastasis between June 1st, 2005, and May 31st, 2010, consulting the Radiotherapy Department in Addis Ababa were included (n=1070). All patient and tumour characteristics and information concerning therapy and outcome was documented from patients' files. From 2006 through 2010, an independent project funded by AstraZeneca Ltd. (Cambridge, UK) facilitated by Axios Foundation (Paris, France) had provided free endocrine treatment (tamoxifen and anastrozole) to patients with positive or unknown Estrogen-receptor status [Reeler 2008]. Information about the programme had been widely distributed amongst institutions, cancer organisations and mass media in Addis Ababa. Due to this unique situation we consider the breast cancer patients at the Radiotherapy Center from 2006-2010 as a representative cohort of patients – presuming that the majority of patients found their way into the programme and came for regular follow-up to receive their endocrine medication. Therapy was recommended according to the Breast Health Global Initiative Recommendations [Anderson 2006a]. The primary endpoint of this study was metastasis-free survival (MFS) since mortality data could not be obtained (patients usually die at home, no death registration available, no phone numbers available). Person time equalled the time from the date of diagnosis to distant metastasis mentioned in the files; women were right-censored at the last documented visit to the clinic. The time of occurrence of distant metastasis was defined as the time point of a positive finding on imaging or of a strong suspicion of distant metastasis by clinical signs (adapted from [Kantelhardt 2014a]).

For the **rural breast cancer cohort**, tissue of all patients operated for suspicious breast abnormalities between 2010 and 2016 was sent to Halle, Germany, for evaluation. In case of confirmed breast cancer, patients were included into the cohort. In case of positive or unknown hormone receptor status, patients received free Tamoxifen. Patients or relatives were personally visited at their homes in 2016 to assess survival status, collect information on compliance to tamoxifen therapy and assess side-effects [Eber-Schulz 2018].

For the **cervical cancer cohort**, women with histologically verified cancer of the uterine cervix (International Classification of Disease-Oncology (ICD-O-3) codes C53.0-9) who were diagnosed and treated between 10.09.2008 and 11.09.2012 at the Radiotherapy Center at Tikkur Anbessa University Hospital in Addis Ababa, Ethiopia, were included. Treatment consisted of radiotherapy and/or surgery. All patient characteristics, tumour characteristics and information concerning therapy and outcome were documented from patients' files. All patients with telephone numbers available were contacted by telephone. Information on the date of last contact and

survival status was obtained by telephone from the patients or – in case of death – from relatives. In case patients or relatives were not reached by telephone, the last date of personal contact was taken from the patients' files. Patients with cervical cancer were referred from all over Ethiopia to Tikkur Anbessa University Hospital for radiotherapy. In Tikkur Anbessa University Hospital the only cobalt-60 teletherapy in the country was available. The surgical treatment was radical hysterectomy with pelvic lymphadenectomy (following Wertheim). Adjuvant, radical and palliative radiotherapy was applied [Kantelhardt 2014b].

3.3 Performing a retrospective study in the context of Ethiopia

For both, the urban breast and cervical cancer cohorts, patient files were retrieved from the archive. The **archive** is a central institution at the university hospital. The rural Aira hospital also uses paper-based patient files which are manually stored. One general challenge was retrieval of the files. Due to miss-placement, incorrect spelling of names or numbers as well as current use of the files by other departments, for breast cancer of 2,031 registered patients 1,507 files were retrieved, of which 1070 fulfilled the inclusion criteria. For cervical cancer of 1,837 patients registered and 1,400 treated, only 1,012 files were retrieved. We considered this proportion of about 3/4 and 2/3 retrieval higher than expected, being aware of the huge challenges faced in the setting. For the rural breast cancer cohort, all patient files were traced prospectively.

As the urban patients were treated and documented during routine care, **documentation** was not standardised. But since there were only one and later three oncologists in the department, even without written standard operating procedures, the information available was similarly documented by the small number of physicians. In Ethiopia there is a hierarchical health care system where patients start consultations at primary level (health center with a nurse available), then go to the regional hospital with general practitioners and possibly a surgeon and then they are sent to a referral hospital (Addis Ababa University Hospital providing the only oncology center). This three-tier referral system may lead to a considerable amount of waiting time between first consultations and actual start of therapy. As the patients often only have a limited education, time points and time periods are often not very precise. We noticed that sometimes there was contradicting information, e.g. a time point of first detection of the disease after the time point of first consultation, etc. We therefore used calendar dates from pathology forms or date of surgery mentioned. Note that additionally the simultaneous use of the international (Gregorian) and Ethiopian calendar (approximately 7 years and 3.7 months difference) added challenges to all estimations of time. Probably there are mistakes of dates in both directions (too early and too late) so we do not assume resulting large bias.

The fact that the majority of patients are taken home by the family once the health situation seems incurable and lack of formal death registration make information on any death difficult to obtain. The option to use mobile phone technology and inquire from patients/relatives has drastically improved knowledge on **outcome**. Since for cervical cancer patients the phone numbers had been documented for a long time (they are called while waiting until a time slot is available for radiotherapy), survival status was obtained for these patients. Phone numbers were not available for urban breast cancer patients, so we used documented evidence in the patient files on distant metastasis as primary endpoint. Individual visits to the rural patients assured precise information on their survival status.

3.4 Statistical analysis

The primary endpoint of the studies was distant metastasis-free survival (MFS) for urban breast cancer, and overall survival for rural breast and cervical cancer, respectively. Person time equaled the time from the first day of radiotherapy to metastasis or death respectively, censoring or to closing date, whichever came first. Probabilities of overall survival were estimated using the Kaplan-Meier method. The 95% confidence intervals (95% CIs) at years one and two were shown. The Cox proportional hazards model was used with the minimal sufficient adjustment set (confounders available and identified by directed acyclic graphs). Analyses were conducted using SPSS® Statistics, version 24 (SPSS, Inc., an IBM Company). Right censoring was assumed to be unrelated to the risk of death. As most of the urban patients were censored, an additional worst-case analysis was performed: all patients who did not attend their appointment within six months after last being seen at the university hospital, were assumed to have died one day after the date of last contact.

3.5 Treatment guidelines and definitions of staging

Due to the efforts within the Ethiopian Breast Cancer Project 2005-2010, resource-adapted **guidelines on breast cancer** from the Breast Health Global Initiative [Anderson 2006a] had been adapted to Addis Ababa radiotherapy center. The rural Aira hospital only provided surgery without any adjuvant therapy during that time. According to international coding standards for cancer registries [Jensen 1991], date of incidence was defined as the first consultation at a hospital for the cancer in question. Information of tumour size (T) and nodal status (N) was used to derive stage by the American Joint Committee on Cancer staging system AJCC (seventh edition) [Edge 2010; Sobin 2009]. All staging information mentioned within the first three months after primary diagnosis was used. T-stage: The pathologist's description was used preferably to the clinician's description. In case of a clinical T4 description, this was given priority over any pathological T. In case of neoadjuvant chemotherapy, cT assessed before chemotherapy was used. N-stage: The

information on lymph nodes from the pathologist was used preferably, if lacking, cN was used. Any positive lymph node described indicated N+. Contralateral regional lymph nodes clinically noticeable without evidence of a local contralateral disease were considered to be distant metastasis. M-stage: Lack of clinical symptoms or radiologically confirmed distant metastasis at diagnosis was considered to indicate a state free of distant metastasis. Tumor histology was classified according to written notes from pathology reports as ductal not otherwise specified (NOS), lobular and for all others summarized other/unspecified [Kantelhardt 2014c].

Patients with early stage **cervical cancer** were surgically treated by radical hysterectomy with pelvic lymphadenectomy (Wertheim). This was done in case of FIGO Ia, Ib and in few cases of patients with FIGO IIa. Addis Ababa University was the only hospital in Ethiopia regularly performing Wertheim surgery (done in 70.8% of the patients operated for cervical cancer) and the only facility administering combination radio-chemotherapy. Adjuvant radiotherapy was given for patients after surgery without clear surgical margins or positive lymph nodes and or parametrial involvement. The patients received 40 Gy in 20 fractions within 4-5 weeks for the first phase. Depending on tumour response, adverse effects and compliance of the patients around 20-26 Gy in 10-13 fractions were applied within 2-3 weeks for the second phase. In case of FIGO IIB or IIIA, primary radical radiotherapy was given. The patients received 46 Gy in 23 fractions within 5-6 weeks for the first phase and 26 Gy in 13 fractions within 2-4 weeks for the second phase. Patients with FIGO IIIB or 4A without bilateral hydronephrosis or clinical fistula were given non-radical radiotherapy with a larger dose per fraction: 32 Gray in 8 fractions within 4 weeks and 18-12 Gy in 6-4 fractions respectively within 2-3 weeks. In case of FIGO IVa or IIIb with bilateral hydronephrosis, IVa with clinical fistula or FIGO IVb the patients received two "single shots" of 10 Gy and depending on response performance status and site of metastasis received additional radiotherapy or palliative chemotherapy. Single shots were also performed because of short waiting time for patients with no option to wait for radiotherapy in Addis Ababa due to their socio-economic background. Haemostatic radiotherapy (12 Gy in 4 fractions) was done independently of FIGO stage, but because of massive vaginal bleeding and decline of haematocrit. Curative chemotherapy simultaneous to curative radiotherapy or neoadjuvant to surgery (cisplatin, 60 mg/m², 3-6 cycles) was recommended, just as palliative chemotherapy with cisplatin and 5FU (50 mg/m², 6 cycles) in cases of patients with FIGO IIIa – IVb. Due to limited availability of the substances and financial limitations of the patients, chemotherapy was not administered on a regular basis [Kantelhardt 2014b]. Staging of cervical cancer patients was clinically using FIGO classification [Pecorelli 2009].

3.6 Tumour biology

We were able to collaborate with the Addis Ababa department of pathology to perform studies on tumour biology. There were also attempts to investigate human papilloma virus (HPV) in **cervical cancer** patients – but the quality of the tumour specimen was not sufficient. Later a study on HPV in healthy women was conducted; publication is pending. Therefore, this thesis focusses on breast cancer biology.

Knowledge about Estrogen-receptor status in **breast cancer** is of high interest to the clinician since this may be a therapeutic target which is cheap and has little side effects: tamoxifen. A large meta-analysis conducted on 10,000 breast cancer patients with luminal breast cancer subtypes showed that adjuvant (i.e., post-primary) treatment with five years of tamoxifen greatly reduced recurrence rates within the first ten years (RR 0.53 (SE 0.03)**.** The effect of chemotherapy was of the same magnitude (RR 0.640-0.84)[Peto 2012]**.** As mentioned above, several studies have pointed out that breast cancer in Africa occurs in young women, at advanced stage and presents as aggressive disease showing high proportions of Estrogen receptor-negative disease. Next to limited treatment options, this may be a reason for the unfavourable outcome of the patients. Breast cancer is composed of different 'intrinsic subtypes' differing from one another in clinical outcome, response and resistance to systemic therapies [Parker 2009]. The luminal-like subtypes express Estrogen (Estrogen receptor+) and Progesterone receptors (+), use Estrogen for growth, and represent the majority (60-70%) of cases in developed country populations. Lower percentages of luminal-like subtypes in African populations have been reported. These findings may reflect genuine regional biologic variations or poor tumour processing and fixation resulting in false Estrogen receptor-negative results [Eng 2014].

To study the tumour biology of breast cancer in Ethiopia, we selected patients with Estrogen-receptor status determined in Addis Ababa and data available from the Addis Ababa hospital-based cohort mentioned above. A total of 352 patients diagnosed between June 2005 and December 2010 were included. The influences of age, stage, and histology on the probability of Estrogen-receptor negativity were assessed by a log-linear regression model. Additionally, we assembled cohorts from Gezira, Sudan, and Halle, Germany, consisting of 560 and 932 patients, respectively, and known hormone receptor status as well as clinical data. We compared the separate cohort of breast cancer patients from East Africa with our own Halle samples [Sengal 2017].

3.7 Summary

In summary, we started our project on female cancer in sub-Saharan Africa performing a thorough systematic literature review on therapy and outcome of breast and cervical cancer in Africa. Then we studied characteristics, treatment and outcome of three large hospital-based cohorts of urban and rural Ethiopian women with breast and cervical cancer. For further insight into possibly unique tumour biology in Africa, we assessed the distribution of positive and negative hormone receptor status in patients with breast cancer from Ethiopia. We analysed clinical and pathological factors which were associated with hormone receptor-positive disease.

4 Results

4.1 Literature search

By searching for “breast/cervical cancer” and “Africa” we identified a total of 7154 publications of which we found 6174 in the large databases MEDLINE (by OVID; 26.03.2014; n=5745) and Cochrane (27.03.2014; n=429) and 980 in smaller databases (AJOL; 23.04.2014, n=281), African Index Medicus (07.05.2014; n=153), The Breast Health Global Initiative (07.05.2014; n=99), POPLINE (09.05.2014; n=340), SurvCan (22.05.2014; n=107). In total, 219 publications were thought to be of relevance and full papers were assessed; these were included in the published review.

In the following, the analysis of publications on breast cancer is presented. In general, we noted an increase in the number of publications available in the databases searched, from 15 articles in 1995–1999 to 72 articles in 2010–2014. The majority of papers (n = 75) originated in North Africa (population in 2012: 207 million), closely followed by West Africa (n = 71; population in 2012: 320 million). Southern Africa (n = 42; population in 2012: 58 million) dominated before the year 2000. There were few publications from East Africa (n = 19; population in 2012: 352 million) and Central Africa (n = 6; population in 2012: 133 million), but the number of studies has increased since the 1990s. This may reflect the socioeconomic development of the countries and the availability of advanced medical service, particularly in the North African region. When comparing the number of physicians per population, there are notable differences seen in the large countries of each region. Egypt and Algeria had the highest numbers (2.83 and 1.21 per 1,000 people in 2008 and 2007), South Africa had 0.77 per 1,000 people in 2004, Nigeria had 0.395 per 1,000 people in 2008, and Ethiopia and Tanzania had only 0.022 and 0.008 per 1,000 people in 2007 and 2006 [www.gapminder.org 2015]. This reflects the focus of primary healthcare mainly involving non-physicians in East Africa (e.g. Tanzania), as opposed to a more clinical approach with more physicians in West Africa. Since there are fewer physicians in East Africa, this can possibly explain the relatively low number of articles on breast cancer therapy from this region.

Looking at the individual countries, we noted that Nigeria was the number one country in terms of the overall number of publications, specifically since 2005. Before 2005, South Africa was the country with the most articles available. It is possible that the case of scientific misconduct during the high-dose chemotherapy breast cancer trial from South Africa may have led to reduced activities in breast cancer research [Horton 2000]. Egypt, Morocco, Tunisia, and Ghana followed

with an overall number of 10 or more articles. The higher numbers of publications also correspond to large population size and advanced socio-economic status of regions.

The therapies described in the articles were mainly surgery (70%), followed by chemotherapy (60%), radiotherapy (46%), and endocrine treatment (38%). Targeted treatment was rarely described. Most publications presented descriptive studies (43%). Meta-analysis or randomized controlled trials were rare (20%). When describing therapy, outcomes as well as side effects are of high interest. About half the studies were able to provide information on the influence of therapy and one fifth informed on side effects (see publication [Kantelhardt 2015]).

In conclusion, from our literature review we found a general gap of literature on breast and cervical cancer in sub-Saharan Africa. Specifically, East and Central Africa had only very few publications. This encouraged us to continue the retrospective studies on presentation and outcome of breast and cervical cancer patients in Ethiopia. From there, therapy implementation studies in a randomized design were planned. Since 2018, an institution-based cluster randomized trial to improve access to endocrine treatment by training breast nurses in eight rural hospitals is ongoing (PhD candidate Mr. Sefonias, Halle and Addis Ababa).

4.2 Breast cancer patients in an urban hospital cohort in Ethiopia

The urban hospital cohort has been described in the publication [Kantelhardt 2014a]. Of 2,031 registered patients at the Addis Ababa University Hospital Radiotherapy Center, 1,507 files could be retrieved. Overall, 1,070 women fulfilled the inclusion criteria. Nearly all patients (n=930; 87%) received an operation. Of those, the majority had modified radical mastectomy (n=880; 95%). Of these, an estimated 20% were operated at the Department of Surgery at Addis Ababa University Hospital. In 628 surgery reports describing the margins, 69.9% reported surgical margins free of disease and 30.1% had margins involvement (for 302 patients (32%), no information on margins was available). The majority of patients (n=893; 83%) also received chemotherapy, mainly anthracycline-containing chemotherapy (n=782). Of these, about 70% were administered at the Addis Ababa University Radiotherapy Center. The preferred anthracycline-containing regimen was FAC (5-fluorouracil 50 mg/m^2, Adriamycin 50 mg/m^2, cyclophosphamide 500 mg/m^2) for 666 patients, AC (5-fluorouracil 60 mg/m^2, Adriamycin 60 mg/m^2) for 116 patients, and for 76 patients cyclophosphamide, methotrexate and 5-fluorouracil (CMF) was used. In general, taxanes were not available. Of all chemotherapy patients, 753 patients (83.7%) received a full six cycles of chemotherapy, mainly FAC (n=577). There were 42 patients who received neoadjuvant chemotherapy. All endocrine therapy for positive or unknown receptor status (n=864)

was administered at the Addis Ababa University Radiotherapy Center. Patients' everyday compliance to endocrine treatment could not be assessed. Adjuvant treatment (if applied) was given rather well-timed; 79% of patients with chemotherapy started within six months and 77% of patients with endocrine therapy started treatment within twelve months after surgery.

In 285 women (26.6%), distant metastasis occurred during follow-up. The majority of women came for regular follow-up visits ranging from 8.1 months to 65.6 months after primary diagnosis (median 23.1 months). Altogether, 101 women (9.4%) did not have any follow-up visit (after completion of therapy: maximum 8 months after the date of diagnosis) and 130 women (12.1%) had incomplete follow-up later on. At the end of the study, 78% of women had complete follow-up.

The age of the women ranged from 20 to 88 years (median age 43.0 years), women aged 30–39 being the largest group of the study population (37.9%). Almost half of the women were premenopausal (49.7%; n=889 information available). Among the women, whose origin had been specifically inquired when their history was taken, half were classified as Addis Ababa and half as non-Addis Ababa residents. The majority of women presented with stage 3 disease. Nodal status was positive in 81% of cases. The most frequent histological type of breast cancer was ductal carcinoma NOS. About half of the women had a pathology report showing grade 2.

To visualize the problem of a bias due to incomplete follow-up information within certain patient groups, distribution by prognostic factors was analyzed. In most subgroups similarly the proportion of incomplete follow-up was around 20%.

MFS of patients after two and five years was 74% and 46%, respectively. In our worst-case analysis, MFS declined to 59% and 27%, respectively. The difference between documented results and worst-case analysis was less than 20% for both, two- and five-year MFS. Worst-case analysis assumed that patients not remaining in care (who had not visited for >6 months) had incomplete follow-up. All patients with incomplete follow-up were considered to have distant metastasis three months after their last visit. To find out the factors influencing MFS, hazard ratios (HRs) were calculated for the different patient characteristics. MFS was highest in women aged 50–59 years and was lower in younger age groups. Women aged 60 years and above also tended to have worse prognosis compared with those aged 50–59 years. The HR for distant metastasis of patients <30 years of age was higher (HR=3.20, 95% CI 1.99–5.14) compared with that of women aged 50–60 years.

Tumor histology was grouped as ductal NOS, lobular, and other/unspecified (e.g., four phyllodes tumours, two sarcomas, medullary carcinoma). Patients with ductal histology had the best MFS compared with the other entities. The lobular group also included specified lobular cancers; outcome was not as beneficial as expected for pure lobular cancers. Women with stage 3 disease had a considerably worse MFS than patients with stage 1/2 disease, showing an HR of 2.62. Women with unknown stage had MFS between those with stage 1–2 and stage 3 [Kantelhardt 2014a].

4.3 Breast cancer biology

The results of our tumour biology study has been published in [Kantelhardt 2014c]. We analysed patients with Estrogen-receptor status available for associations of hormone receptor status and other tumour and patient characteristics. First, we compared characteristics between the total population of 1,208 patients and the subgroup of 352 patients with Estrogen-receptor results available. The distributions of place of origin, menopausal status, histology, and adjuvant therapy were similar. Patients with Estrogen-receptor results available were more often under 30 or over 60 years of age, and also tended to have a higher stage at diagnosis than patients with Estrogen-receptor results not available. Due to the preferred procedure of staining FNAC to determine Estrogen receptor, patients with Estrogen-receptor results available had more often FNAC done for their pathological diagnosis.

Within the subgroup of patients with Estrogen-receptor results available, 34.7% (95% CI 28.9–38.8%) had Estrogen receptor-negative findings. The prevalence of Estrogen receptor-negative findings was associated with patients´ age. Based on a log-linear regression model, the estimated stage-adjusted prevalence of Estrogen receptor-negative findings decreased for each additional five years of age by 6% (PR=0.94, 95% CI: 0.89–1.00), note the CI is close to 1. Progesterone receptor was positive in 72% (162/224) of Estrogen receptor-positive tumours and 12% (14/120) of Estrogen receptor-negative tumours.

None of the other patient characteristics, including place of origin outside Addis Ababa, stage and histology, was associated with the prevalence of Estrogen receptor-negative results. Results from the FNAC specimen as compared to the tumour specimen had a lower age- and stage-adjusted prevalence-ratio for Estrogen receptor-negativity (PR=0.71; 95% CI: 0.51–0.98) [Kantelhardt 2014c].

Seeing this data from the central referral hospital in Addis Ababa, we were also interested in the situation in the countryside. Our corresponding cohort is published in [Eber-Schulz 2018]. With

the hypothesis that also there patients are likely to have a positive hormone-receptor status, we suggested that endocrine therapy would be an excellent option for all those rural patients who are financially unable to find their way to the capital city. In our rural breast cancer cohort we found that of 107 patients diagnosed with breast cancer there were 65.8% with positive Estrogen receptor or Progesterone receptor PgR status. Since 2013 we run a donation project to provide free Tamoxifen for those rural patients with limited financial resources. Outcome was assessed in 2013 and 2015, when a medical student visited all patients at their homes. Adverse survival was associated with lymph node involvement, tumour size, and HR status [Eber-Schulz

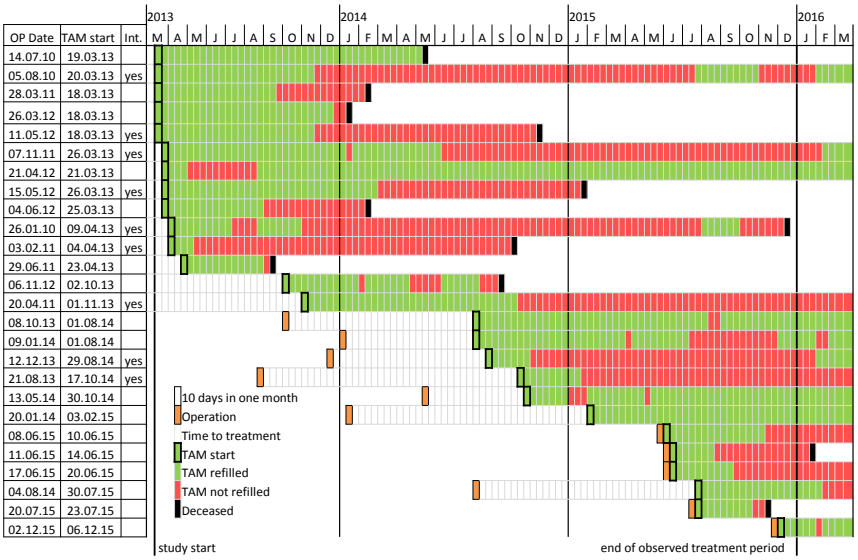

Figure 4: Illustration of the refill results of patients between 26.3.2013 and 10.3.2016. Abbreviations: TAM, Tamoxifen; Int. Interrupted; OP operation. (unpublished)

2018].

Of 51 eligible patients, 26 started Tamoxifen therapy (figure 4, unpublished). Adherence after one year came down to about 50% (figure 5). Therefore, we now started a research project to assess improvement of adherence by introducing breast nurses in four hospitals and compare to four hospitals without intervention (PhD project Sefonias Getaches, 2018, funded by Susan Komen Foundation).

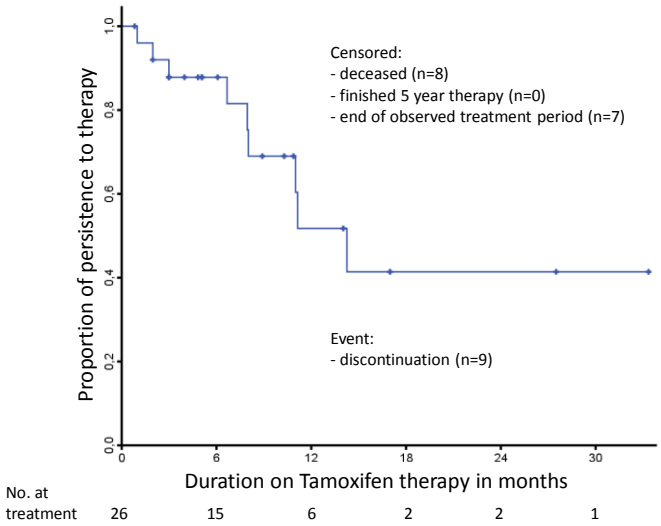

Figure 5: Kaplan-Meier estimates of lost-to-follow-up in months of treatment with Tamoxifen. Discontinuation: no patient contact for more than 6 months (unpublished).

4.4 Cervical cancer patients in a hospital cohort in Ethiopia

The cervical cancer patient cohort study has been published in [Kantelhardt 2014b]. Between 10.09.2008 and 11.09.2012 an estimated 2,300 patients with cancer of the cervix uteri were registered at the Addis Ababa University Radiotherapy Center. This included 103 patients who had received surgery for the cancer. Of those, 1,837 were seen by the radiation oncologist, and radiotherapy was planned. The estimated number of patients who received radiotherapy was 1,400. Out of those, 1,012 patient files could be retrieved. A further 47 patients who only received surgery for early-stage cervical cancer were included in the study. Note that an estimated 900 patients who registered never received any therapy [Kantelhardt 2014b].

Most patients came from rural areas (56.5%). The largest group of patients were 40–49 years old (30.9%). The majority of patients (78.1%) were postmenopausal. The mean number of children was 6.0, with 10% and 90% percentiles of 2 and 10, respectively. Many women reported only one lifetime sexual partner (52.7%) as well as marriage before the age of 18 (83.9%). The proportion of women using contraceptives was 31.1%. A total of 9.4% were known to be HIV-positive. The Eastern Cooperative Oncology Group (ECOG) performance status 1 at first presentation was common (57.8%). The largest group of patients presented with FIGO stage IIb–IIIa (46.7%) and squamous cell carcinoma (93.4%).

An important piece of baseline information was change in FIGO stage between pathological diagnosis and the start of radiotherapy, during which time a considerable number of patients died while waiting for treatment. However, information about these patients was not available. Due to the huge patient load, the median waiting time was 1.8 months between first registration at the Radiotherapy Center and first appointment with a radiation oncologist (10^{th} and 90^{th} percentiles were 0.2 and 5.2 months, respectively). The median waiting time between appointment with a radiation oncologist and start of radiotherapy was 0.2 months for emergency radiotherapy, 1.7 months for radical radiotherapy, and 2.3 months for non-radical radiotherapy. The proportion of patients with advanced stages IIIb and above increased between appointment (33.5% stage IIIb-IVa) and start of radiotherapy (63.9% stage IIIb-IVa).

The majority of patients received radiotherapy; only 4.4% received surgery (only for early stages of the disease). Out of 158 patients receiving surgery, the majority (n=143; 70.8%) received radical hysterectomy, six received simple hysterectomy and nine surgeries were of unknown extent. Non-radical radiotherapy was administered to almost half of the patients. Due to the lack of finances or availability of drugs, only 96 patients received simultaneous radio-chemotherapy.

Within the whole cohort, a total of 212 deaths were registered. Another 37 patients were reported dead at the time of telephone interview, but the date of death remained unknown. Therefore, these patients were entered as alive and censored at the time of last personal appointment documented in the files. A total of 378 patients were lost to follow-up. Therefore, a worst-case analysis was performed (see methods). The estimated overall survival was shown for the total patient cohort. The estimated one- and two-year survival probabilities were 90.4% and 73.6%, respectively (note that the number of patients under observation was only eight at the end of year three). In the worst-case analysis the estimated two-year overall survival declined to 45.40%. The median survival time was 40.6 months, declining to 21.5 months for the worst-case analysis.

The estimated two-year overall survival was most favourable for patients with stages FIGO Ia–IIa disease at the time of first presentation (84.8%, or worst-case 66.7%). Patients with stage FIGO IIb–IIIa had lower (79.5%, or worst-case 53.1%) and patients with stage FIGO IIIb–IVa the lowest (55.8%, or worst-case 25.3%) estimated overall survival probabilities after two years. There were only a few patients with stage FIGO IVb disease (n=7). Twenty-eight patients experienced recurrence. These cases together had an estimated two-year overall survival probability of 54.6%, or worst-case 32.7%. Those patients represent a heterogeneous group with a rather unfavourable survival probability. Comparison of the FIGO stages showed relevant differences in survival probability between stages ($p<0.001$).

Additionally, data was analysed according to completeness of therapy stratified by radiotherapy schedule. Only those patients were included who received a standard therapy schedule (radical, non-radical and palliative schedule) according to the stage of their diseases. Discontinuation of radiotherapy was associated with reduced overall survival. For radical radiotherapy there was a trend (HR 1.3) to reduced survival; for non-radical and single fraction schedules there was a significantly reduced survival with a HR of 3.1 and 7.3, respectively, for those patients who discontinued radiotherapy. This severe impairment in outcome for patients who discontinued their radiotherapy schedule was still present when performing the worst-case analysis. Of course, due to the retrospective nature of the study, a causal relationship between discontinuation and adverse outcome cannot be proven [Moelle 2018].

5 Discussion

Cancer has been a neglected health topic in Africa for a long time. Due to the increase in activities of population-based cancer registries, cancer incidence rates become more and more available. Data for 2012 from 26 African countries [Ferlay 2018] suggest that in the majority of countries breast cancer is now the number one cancer among the female population, closely followed by cervical cancer. This underlines the necessity to set the ground for evidence-based preventive and therapeutic interventions. In Ethiopia there is an increasing interest to improve breast and cervical cancer health care. Within the Addis Ababa-Halle collaboration on female cancer we have aimed to provide data on female cancer care in Ethiopia. This thesis summarizes our results of an initial literature review and then describes characteristics, therapy, and outcome of large breast and cervical cancer cohorts from Addis Ababa University hospital and rural Ethiopia. Also we investigated differences in tumour biology comparing Ethiopian and Sudanese specimen with our Halle, Germany, cohort. We found that endocrine treatment is a highly underutilized, cheap and well tolerable treatment which would be suitable in the Ethiopian setting with a high proportion of endocrine responsive tumours. We have thus recently started an ongoing prospective cluster-randomized trial in eight rural hospitals to improve implementation and adherence to endocrine treatment by training breast nurses.

5.1 Literature review

Our literature search [Kantelhardt 2015] revealed that the number of publications on therapy and outcome of female cancer in Africa is still low but increasing over the years. There was a large number especially from North Africa, whereas there were very few to no publications from central Africa despite of a considerable proportion of the African population in this area. These results probably reflect socio-economic status, political stability, and functioning of the health system of these regions. We note that surgery was the main focus and probably also the most widely applied therapy for breast cancer patients. The observation that 60% of articles analyzed or mentioned chemotherapy may indicate that systemic therapy is also used on the continent. However, the finding that only 38% of articles addressed endocrine therapy indicates an increased need for more focus on this inexpensive and well-tolerated treatment option. In most cases, descriptive studies were conducted. We found less than 10% randomized controlled trials and only one quarter interventional trials. When looking at level of evidence (LoE) criteria according to the Oxford definition [Phillips 2009], most articles showed LoE 4 (72%). This strongly indicates the need to design and implement more high-quality interventional studies in Africa in the setting of limited resources, specifically addressing young patients with advanced disease and a unique exposure to infectious and chronic co-morbidities.

5.2 Breast cancer characteristics, treatment, and outcome

Our **Addis Ababa urban clinical cohort** was the first detailed and largest study on breast cancer survival in Ethiopia and other parts of sub-Saharan Africa [Kantelhardt 2014a]. Overall, metastasis-free survival (MFS) probability in this cohort of Ethiopian women with breast cancer was 74% after 2 years and 46% after 5 years. Patient characteristics in our cohort tended to be unfavorable compared with Western cohorts; more than half of the patients were premenopausal, age <40 years, and/or with stage 3 disease. Tumor biology was rather favorable; the majority was ductal and grade 2. Often cancer survival data in developing countries do not report MFS, but have the endpoint of overall survival. A report from Uganda showed an overall survival probability for stage 1–2 cancers of 74% and stage 3–4 cancers of 39% [Gakwaya 2008]. Our stage 1 and 2 patients showed 72% and stage 3 patients showed 32% MFS probability, and overall survival is expected to be higher. This possibly points to a more favorable outcome in our cohort from Ethiopia compared with Uganda.

Our **Aira rural clinical cohort** was the first cohort describing breast cancer presentation and outcome in a rural setting in Ethiopia, sub-Saharan Africa. All patients were followed prospectively with home visits to assess survival status. The data shows three quarters young patients with age below 50 years, mostly presenting with advanced disease. Receiving surgery without adjuvant therapy probably prevents local ulcerations, but almost all patients died within five years. This is similar to historical data of untreated patients from the last century in England [Bloom 1962; Johnstone 2000]. Seeing two thirds with receptor positive disease gives hope for improvement by implementation of endocrine treatment.

The low **median age** of 43 and 45 years in our two cohorts, respectively, is a factor of unfavorable prognosis. Age was slightly lower compared with other studies. Generally, young age is a non-modifiable risk factor attributed to the young population structure in Ethiopia. A previous study conducted from 1995 to 1999 on 125 consecutive breast cancer cases from Addis Ababa University Hospital revealed a median age of 40 years [Tessema 2006]. Reports show median ages of 46 years in Mali (n=118), 46 years in Tanzania (n=328), 49 years in Ghana (n=330), and 48 years in Nigeria (n=192) [Ly 2012; Rambau 2011; Ohene-Yeboah 2012; Adebamowo 2008]. We also found poor MFS in the elderly group of women above 60 years of age. Most likely, their general health status is responsible for possibly sub-optimal therapy and a tendency towards poorer MFS in this group.

Additionally, as in other developing countries, a large proportion of our women presented with a **late stage** of the disease. A recent meta-analysis has shown that indeed there are high proportions (between 30% and 100%) of late stage diseases (3 and 4) among case series from Africa. There was no difference between the regions except lower proportions among urban-only populations compared with mixed rural/urban populations. The proportions of late stage decreased over time [Jedy-Agba 2016]. A study with more than 1,000 patients from South Africa showed an association between longer distance between residence and hospital and risk of late-stage diagnosis [Dickens 2014]. We could not confirm this finding when comparing patients originating from Addis Ababa and rural Ethiopia. Definitely, stage at diagnosis is a modifiable risk factor; it can be reduced by awareness, early detection, and screening activities. Screening for breast cancer is still mostly unavailable in Africa, except for South Africa and limited activities in North Africa. A screening approach faces several challenges. One of them is that the majority of women in the population are young women with dense breast tissue. Lack of radiologists, breast surgeons, and facilities to do wire-guided surgery clearly do not allow mammography screening in the majority of African countries. The only feasible option might be the use of clinical examination. A large breast cancer screening programme was evaluated in rural Sudan [Abuidris 2013]. Trained volunteers visited households in 56 villages and screened about 10,000 women by palpation, detecting 138 breast abnormalities, finding nine breast cancers (four early and five advanced) and eight in-situ cancers. In 79 control villages, only four women reported to the hospital of which three had advanced breast cancer. This shows the positive effect of an early detection programme by local volunteers. These results give a perspective on how to possibly intervene on a population level in rural settings with limited service available. Whether in the end it will be more feasible and cost efficient to train volunteers for breast examination or to add breast examination to existing public health programmes like family planning remains an open question.

Tumor biology is also a main prognostic factor. Often, tumours in the African setting were described as aggressive with high grading. In our studies, the tumour biology of female Ethiopian breast cancer patients was favourable: only a small fraction, one third of patients in urban and rural setting, had Estrogen receptor-negative breast cancer [Kantelhardt 2014c; Eber-Schulz 2018]. Older age predicted lower fractions of Estrogen-receptor negativity. All other patient characteristics, especially advanced stage, histology, and Estrogen-receptor results from local recurrence, did not predict Estrogen-receptor negativity. Results from fine-needle aspiration cytology (FNAC) were less often Estrogen receptor-negative than results from tumour specimens. A limitation of our study was that we only tested Estrogen-receptor status on 29% of all the

cases in the cohort. However, this group did not differ much from the total cohort of 1,208 patients in clinical and pathological characteristics. Another limitation of our study was using results from FNAC staining among 36.1% of the cases instead of the gold standard histologic staining. In the cohort, FNAC showed a lower proportion of Estrogen receptor-negative results compared to the gold standard of histologic staining. Even though FNAC is not the gold standard, we believe FNAC staining does accurately reflect the immunohistochemical results for the tumour as comparative studies have shown [Zoppi 2002]. Additionally, Estrogen receptor was sometimes stained on material from local recurrence. Jabbour *et al.* described a 20% variation of Estrogen-receptor expression between local recurrence and primary tumour, rather than switching from Estrogen receptor-positive to Estrogen receptor-negative expression in recurrences. Also, advanced stages rather tended to be receptor negative more frequently [Jabbour 2012]. Therefore, our patient cohort would be expected to have higher false Estrogen receptor-negative expression due to some results originating from recurrence material compared to the original primary tumours. Since our findings show a high Estrogen receptor-positive proportion, this proportion would be even higher in the primary and early-stage tumours often described in studies from the Western world. Therefore, our results might even underestimate the proportion of Estrogen receptor-positive findings. Our study is in line with the findings of Jemal *et al.* [Jemal 2012], showing that U.S. immigrants from East Africa have a high proportion of Estrogen receptor-positive breast tumours similar to Caucasian Americans as compared with West African immigrants. Many previous studies on tumour biology in Africa found small proportions of Estrogen receptor-positive tumours. A recent meta-analysis of African publications revealed >65% Estrogen-receptor positivity in prospectively collected breast cancer patients from Africa. The meta-analysis found that besides design of the study, also proportion of G3 tumours and region of origin influenced the proportion of Estrogen receptor-positive disease [Eng 2014]. Definitely, lack of standardized staining and reading procedures, possible antigen degradation of archived material, and patient selection influenced the results. Seeing high proportions of Estrogen receptor-positive tumours in our study justifies the administration of Tamoxifen in unknown receptor status. This is a crucial in the limited resource setting of sub-Saharan Africa: a personal inquiry within the network of cancer registries revealed that more than half the countries do not have options to perform immunohistochemistry. Additionally, many patients are unable to afford the testing.

A pilot project to implement Tamoxifen therapy in Aira hospital was started after seeing the catastrophic survival outcome (unpublished data). After two years, house-to-house visits were performed again to assess uptake and persistence of therapy. Persistence to therapy was 52%

after one year. Principally endocrine treatment seemed feasible, but lack of pathology service, financial and organizational barriers were identified. Most patients who took Tamoxifen had advanced disease and probably occult metastasis. Hence, survival was short despite the treatment – this will not encourage new patients to take the medication. Long-time survivors are urgently needed to educate the population. Improvements of system-wide issues at health institutions are also crucial to gradually implement primary oncology care in the rural setting.

Adjuvant treatment will positively influence the outcome of breast cancer patients according to current evidence. We found that in urban Addis Ababa the majority of patients received adjuvant treatment according to the standard BHGI guidelines from 2006, which recommend anthracyclines and tamoxifen (for positive and unknown hormone receptor status) for this setting with limited resources [Anderson 2006b]. Adjuvant therapy was done in a standardized manner at the Addis Ababa University Radiotherapy Center for the majority of patients. Surgery was mainly modified radical mastectomy for nearly all patients. The fact that nearly 80% of surgery was done in peripheral hospitals might account for low yield of lymph nodes (LNs) probably due to suboptimal surgical techniques. There are published data about the adequacy of surgery in peripheral hospitals from India. Thorat *et al*. reported that out of 424 referred cases, 153 were re-operated due to clinically suspected inadequate removal of tumour [Thorat 2008]. Of those, 64 patients were diagnosed with additional involved LNs; no tumour was found in remaining breast tissue. Therefore, in our cohort from a similar setting, there might be a considerable proportion of patients with involved LNs in situ. Additionally, there were 140 patients who did not receive any surgery due to a lack of plastic surgery options. These patients did receive chemotherapy. Altogether, our cohort consisted of about 700 patients who received optimal care with mastectomy, anthracyclines, and endocrine treatment.

Differences in breast cancer-specific survival of **various ethnic groups** have been described. This could possibly be another reason for unfavorable outcome of our Ethiopian cohort compared to Western data – even though lack of adequate therapy is most probably the most important problem in Ethiopia. Among US citizens, Caucasian women have the best, African-American women have the poorest, and other immigrants have intermediate breast cancer-specific survival – though reports show small absolute differences [Maskarinec 2011]. Possible factors that contribute to these differences are unfavorable stage at diagnosis, limited access to care, comorbidities, socioeconomic status, obesity, and physical activity. Additionally, genetic factors may lead to differences in tumour biology and thus outcome – taking into consideration that women of African origin have a much more diverse genetic background not yet well studied compared to Caucasian women [Akarolo-Anthony 2010; Brinton 2014; Jakobsson 2008]. Also, the lack of

awareness, low economic status, lack of knowledge, etc. may result in reduced treatment uptake [Dye 2011].

There are some factors that **limit** our results. We have to assume that patients with low income, probably mostly from rural areas, may not reach the Addis Ababa University Radiotherapy Center or other treatment facilities. Therefore, this cohort is probably exclusive of very poor patients, especially those living further away. It is possible that this group that hardly accesses the health care system would present late, have less compliance, not remain in care, and therefore add to the unfavorable higher stage group with reduced survival probabilities. Second, our urban cohort showed a considerable proportion of women with incomplete follow-up (21%). Therefore, the assumption of right-censoring being independent of time to distant metastasis may not be valid. By analyzing the time pattern of right-censoring in incomplete follow-up patients within prognostic groups, we found no differences between prognostic groups. However, this does not prove the above-mentioned assumption of independence for the prognostic factors. In a setting without valid endpoints like vital registration and with a retrospective design, these doubts cannot be ruled out. For sensitivity analysis, all patients with incomplete follow-up were considered to develop distant metastasis three months after their last appointment. The resulting differences in MFS did not differ among the subgroups of the prognostic factors of interest. Therefore, we believe that potential bias was not substantial, although we are aware that these observations cannot exclude that right-censoring was related to the risk of distant metastasis.

5.3 Cervical cancer characteristics, treatment and outcome

We presented a large cohort of patients who received oncologic therapy for cancer of the cervix uteri [Kantelhardt 2014b]. With a median follow-up time of 16.5 months (for surviving patients), the overall survival was 90.4% and 73.6% at one and two years, respectively. In total, about half and one third of the patients presented with stages IIB–IIIA and stage IIIB, respectively. We found several months long waiting times until the start of radiotherapy leading to even higher proportions of patients with late-stage disease by the time radiotherapy was started.

Cancer survival data from Africa is mainly based on cohorts from national or regional population-based registries. Therefore, we discuss our data with respect to these published results. It should be noted that the registry cohorts aim at including all cases irrespective of stage of disease or whether treatment was received. Our cohort lacks late-stage patients who died before the start of therapy and poor patients unable to pay for therapy (n=900). Therefore, due to the nature of our cohort, survival was expected to be more favourable compared with population-based data.

Data from the population-based cancer registry of Kampala/Uganda show a five-year age-standardized survival of 19% in 1993–1997 [Wabinga 2011]. The Harare/Zimbabwe cancer registry (n=284, half treated with radiotherapy) found a three-year overall survival of 44.2% [Chokunonga 2004]. Sankaranarayanan *et al.* report a five-year overall survivals of 22% and 13% in Gambia and Uganda, respectively [Sankaranarayanan 2010]. In our study we found a two-year overall survival of 74%, which is higher than the data from Zimbabwe and considerably better than the data from Gambia and Uganda. This higher survival may point to a positive radiotherapy-treatment effect besides the lacking late-stage patients in our cohort.

Looking at high-income countries, Petereit *et al.* reviewed treatment results in 5,619 patients receiving external beam radiotherapy followed by high-dose brachytherapy as reported in original publications between 1985 and 1997. The FIGO stages in their cohort were comparable to our cohort. The overall five-year survival probabilities were higher than our findings: 85%, 68% and 47% for FIGO stages I, II and III, respectively [Petereit 1999]. The lack of brachytherapy in our cohort may explain the observed lower survival probabilities. Due to early detection activities, many pre-cancerous lesions have been discovered and treated leading to reduced incidence. Those patients who still develop cancer indeed also in higher income countries show unfavourable survival probabilities. The African-American population from the SEER database showed an overall five-year survival of 58% [Howlader 2018].

Late stage at presentation is a major prognostic factor for decreased survival which is potentially modifiable. In our cohort, 34.2% of the patients were diagnosed at FIGO stage IIIB and above. This is comparable with data reported from Cape Town/South Africa, where screening was not available between 1984 and 2000 [Denny 2012a]. As an example of a country with high screening activity, data from Germany showed that 66% and 22% of the women presented with T1 and T2 tumours, respectively [Robert Koch-Institut 2012]. Due to the lack of screening opportunities in Ethiopia, patients usually present late with symptomatic disease. Additionally, waiting times from presentation to hospital until start of radiation therapy strongly contribute to stage migration.

When discussing radiotherapy dose, it must be considered, that Addis Ababa University is the only institution in Ethiopia providing radiotherapy. At the time our study was conducted, brachytherapy was not available and external beam radiotherapy was performed by means of a Theratron Equinox 80 Cobalt-60 unit with a source-to-surface-distance of 80 cm. Mostly due to methodological shortcomings, studies on a radiation dose-response relation for cervical cancer patients had controversial outcome [Petereit 1999]. However, in case of radiotherapy for prostate

cancer, there is clear proof for better survival in case a certain dose threshold (78-80 Gy) is reached [Eade 2007]. Correspondingly, Beskow *et al.* demonstrated better survival along with dose increase for cervical cancer patients [Beskow 2012]. Most patients included in the present study were staged FIGO IIIB, which has been shown to respond well to high-dosage external beam radiotherapy [Petereit 1999; Lanciano 1991 #6691]. However, our FIGO IIIB and IVA staged patients received a low-dose hypofractionation non-radical schedule with a maximum of 14 fractions, thus only 14 treatment days, compared to 36 fractions for radical radiotherapy, allowing for a larger number of patients to be treated. To that effect, the limited availability of radiotherapy, regardless its modality, needs to be addressed as main obstacle. In Africa, Ethiopia shows the second largest gap between offer and demand for radiotherapy machines after Nigeria. Judging from the WHO recommendations, there are 73 radiotherapy units missing in Ethiopia [Abdel-Wahab 2013]. This serious quantitative deficit should be addressed first, before insularly enhancing radiotherapy quality with complex techniques.

For the meantime, our data show higher survival in case of guideline-conform radiotherapy. Most known discontinuations were due to radiation toxicities. Hence, better supportive therapies and more brachytherapy need to be made available. However, a larger number of patients discontinued for undocumented reasons which is most likely due to financial and logistical obstacles [Hailu 2013] or breakdown of the radiotherapy machine. Socioeconomic support for patients in need, reliable maintenance services with available spare parts and more radiotherapy machines are necessary for better therapy adherence.

Regarding radio-chemotherapy, most patients at Tikkur Anbessa University Hospital did not receive the recommended concurrent or palliative chemotherapy along with radiotherapy. The facts that a larger proportion of cancer patients in sub-Saharan Africa might not be fit for platinum-based chemotherapy [McArdle 2007] and that adverse effects can be difficult to control do not sufficiently explain the lack of chemotherapy in 85% of all patients observed. We suspect mainly financial obstacles and problems of availability to hinder clinical indications. Hence, the importance of available and affordable chemotherapy for all cervical cancer patients must be emphasized.

Prevention, screening and early detection have been proven useful also in low-resource settings. In Africa, screening with visual inspection and acetic acid combined with immediate cryotherapy of suspicious lesions has been implemented regionally. Recently, the role of HPV testing in screening-programmes is under discussion. Additionally, HPV vaccination has become a possible option for primary prevention [Ginsburg 2017]. In Ethiopia there is little awareness of HPV and

cervical cancer within society, and symptoms of vaginal bleeding are socially stigmatised. The benefits of modern therapy are still perceived as low [Birhanu 2012]. Vaccination, screening, or early detection are not yet available in normal population [WHO/ICO HPV Information Centre. 2007]. Rwanda has now become the first country in Africa to implement a nation-wide programme including HPV-vaccination, early detection, and screening [Binagwaho 2013]. These options could eventually change the burden of cervical cancer disease in Africa [Ginsburg 2017].

In 2018, a cluster-randomized trial in Southern Ethiopia was started within our collaboration to compare uptake and adherence to procedure of two recommended cervical cancer screening procedures: visiual inspection with acetic acid by a nurse at the hospital and self-sampled specimen send to Addis Ababa laboratory for HPV detection (PhD candidate Mr. Muluken Gizaw, funded by Else-Kröner-Fresenius Stiftung). This trial is ongoing; 1800 women have been screened (up to 27. 11. 2018) and one women with clinically manifest cervical cancer was found.

There are certain factors that **limit** our results. Firstly, there is no clinical information on patients who registered but never saw a physician (estimated n=463). Economic reasons, logistic reasons, or progression of the disease are possible explanations. Other patients (estimated n=437) saw a physician, but never started therapy – the relevant files could not be retrieved. We assume that a number of very advanced cases were not included in this study, leading to more favourable characteristics than in the overall cohort of patients presenting at the referral hospital. Secondly, radiotherapy did not include the application of brachytherapy. This is known to be a sub-optimal standard of treatment. Since half of all radiotherapy departments in Africa are not able to offer brachytherapy, we still consider these findings of interest for countries with limited resources. Despite these limitations, our study is the first to thoroughly characterize and follow >1,000 patients in the clinical setting and therefore adds information about the care and prognosis of cervical cancer in Africa to the literature.

6 Summary

This research aimed to investigate the huge disparity in female cancer care in sub-Saharan Africa, especially Ethiopia. Our literature search on female cancer care in Africa showed that there is only a small number of publications about treatment and outcome of female cancer patients in Africa. There is a trend to more publications per year over time. The majority of studies are descriptive; randomized controlled trials or meta-analyses are lacking especially in East Africa. In our retrospective clinical breast cancer cohort from Addis Ababa University hospital we found two-year metastasis-free survival probabilities of 74%. This underlines that the current local guidelines result in relatively good outcome considering unfavorable patient characteristics of young age and stage 3 tumours. Notably, we only described patients who actually received therapy. We showed that about two thirds of the patients had Estrogen receptor-positive disease eligible for endocrine treatment. This cheap and easy to administer treatment with few side effects seems to be a still highly underutilized option; many publications had mentioned low proportions of Estrogen receptor-positive disease. The evaluation of our donation project in the rural setting showed feasibility of Tamoxifen treatment in a peripheral hospital without an oncologist.

In our cervical cancer patient cohort, we found that long waiting times lead to stage migration, which eventually resulted in a high proportion of late-stage disease. Only 15% of patients received concurrent radio-chemotherapy; brachytherapy was not available. Still the estimated one- and two-year survival probabilities were 90.4% and 73.6%, respectively. We also found that a considerable number of patients discontinued their treatment with a subsequent higher risk for fatal outcome. These data on an individual level reflect the situation of a country with nearly 100 million habitants providing only one radiotherapy unit. There is no doubt about the disastrous effect. To implement a triage system preferably treating very early stage patients seemed urgent, but it was ethically and culturally very difficult according to the Ethiopian colleagues.

In general, clinical breast examination and cervical cancer screening should be incorporated nationwide into low levels of the health system, for example in health centers. There are ongoing governmental activities to provide visual inspection with acetic acid in facilities throughout the country. Additionally, expanding comprehensive clinical service on primary and advanced level is of great importance since increased awareness will lead to a higher number of patients. The Ethiopian cancer care programme needs a strong component of providing accessible surgical and adjuvant treatment to prove a benefit of early breast cancer diagnosis. Staff and patients need to understand the concept of a complex disease and the importance to remain in care for

eventual success of the treatment. Ultimately, long-term survivors must be visible in public to convince about the necessity and individual benefit of treatment. Only this can change the perception of cancer from “fatal diagnosis where anyway nothing can be done” to “cancer: a disease which can be cured”.

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7 Theses

1. Breast and cervical cancer is an increasing cause of morbidity and mortality in women in Africa due to ageing and changes in life style and reproductive behavior. Despite this burden, there are still few but slowly increasing numbers of publications on breast cancer therapy and outcome mainly as level of evidence 4 especially from North Africa (n=33 in 2010-2014) followed by West Africa (n=21 in 2010-2014).

2. Distant metastasis-free survival in a hospital cohort of breast cancer patients from Addis Ababa was relatively good given the limited resource setting (distant metastasis-free survival probability of 74% after two years). Most patients received surgery (87.0%); adjuvant therapy such as chemotherapy within six months (79.1%) and endocrine treatment within twelve months (76.7%) were rather well-timed. Young age (half below age 50 due to the population structure) and advanced tumours (two thirds stage 3) need to be considered to plan cancer control programmes.

3. More than two thirds of breast cancer cases were tested as hormone receptor positive in Addis Ababa (n=352) and similar in a remote rural hospital (n=107). Endocrine responsiveness is therefore an excellent chance to administer Tamoxifen even for patients with unknown receptor status. Health system readiness, patient education, and navigation is crucial to assure adherence.

4. Long waiting times to receive radiotherapy were seen for patients with cervical cancer. Stage migration therefore led to a high proportion of patients with late stage at the beginning of therapy (64% stage IIIB-IVA) compared to the first appointment (34% stage IIIB-IVA). Long waiting times are due to availability of only one radiotherapy machine for the whole country.

5. Lack of brachytherapy (100%) and in many cases lack of chemotherapy (82.9%) for cervical cancer patients show options for improvement of therapy.

6. Analysis of dose and outcome showed that patients up to stage IIIB-IVA receiving a complete radiotherapy course >50 Gy had relatively good one-year overall survival probability of 89%. Those who discontinued their treatment had a worse outcome of 87% (44-50 Gy) or even 71% (14-42 Gy) one-year overall survival probability.

7. Health-system preparedness, patient navigation and financial subside as well as public awareness and visibility of long-term survivors, along with political willingness, may eventually implement comprehensive female cancer care in Ethiopia.

8 Annex

Kantelhardt EJ.; Zerche, P.; Mathewos, A.; Trocchi, P.; Addissie, A.; Aynalem, A. *et al*. (**2014a**): Breast cancer survival in Ethiopia: a cohort study of 1,070 women. In: *International Journal of Cancer.* 135 (3), S. 702–709. DOI: 10.1002/ijc.28691.
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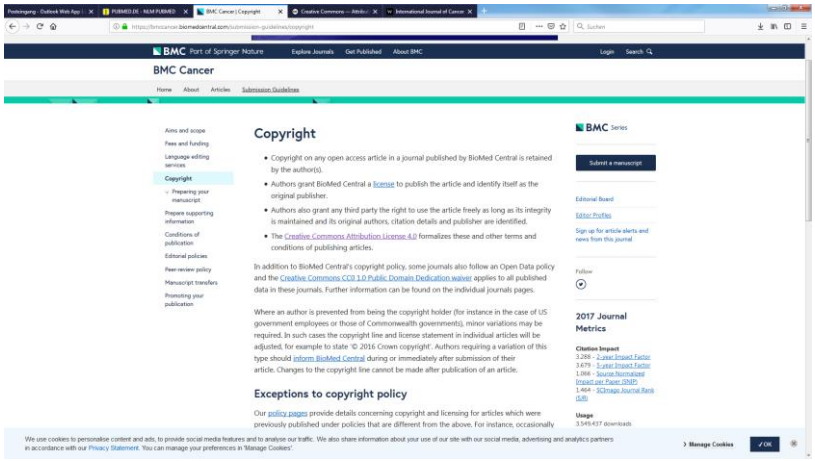

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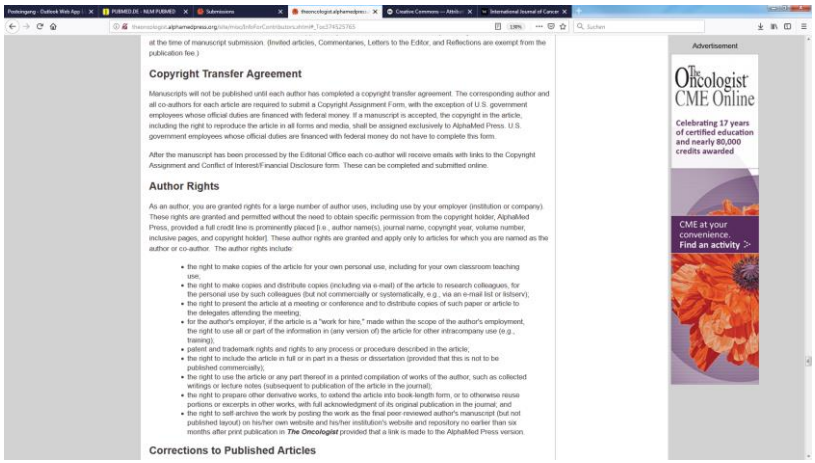

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A Review on Breast Cancer Care in Africa

Eva J. Kantelhardt et al

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The Oncologist®

Global Health and Cancer

Cervical Cancer in Ethiopia: Survival of 1,059 Patients Who Received Oncologic Therapy

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

Key Words. Uterine cervical neoplasms • Africa • Ethiopia • Survival • Prognosis

Abstract

Background. Almost 500,000 women are newly diagnosed with cervical cancer (CC) every year, the majority from developing countries. There is little information on the survival of these patients. Our primary objective was to evaluate consecutive CC patients presenting over 4 years at the only radiotherapy center in Ethiopia.

Methods. All patients with CC from September 2008 to September 2012 who received radiotherapy and/or surgery were included (without brachytherapy). Vital status was obtained through telephone contact or patient cards.

Results. Of 2,300 CC patients, 1,059 patients with standardized treatment were included. At the end of the study, 249 patients had died; surviving patients had a median follow-up of 16.5 months; the 10% and 90% percentiles were 3.0 and 32.7 months, respectively. Mean age was 49 years (21–91 years). The majority of patients presented with International Federation of Gynecology and Obstetrics stage IIb–IIIa (46.7%). Because of progression during the waiting time (median 3.8 months), this proportion declined to 19.3% at the beginning of radiotherapy. The 1- and 2-year overall survival probabilities were 90.4% and 73.6%. If assuming a worst-case scenario (i.e., if all patients not available for follow-up after 6 months had died), the 2-year survival probability would be 45.4%.

Conclusion. This study gives a thorough 4-year overview of treated patients with CC in Ethiopia. Given the limited treatment availability, a relatively high proportion of patients survived 2 years. More prevention and early detection at all levels of the health care system are needed. Increasing the capacity for external-beam radiation as well as options for brachytherapy would facilitate treatment with curative intention. ***The Oncologist*** 2014;19:727–734

Implications for Practice: This study analyzes 1,059 patients from Ethiopia with newly diagnosed cervical cancer who were treated by radiotherapy in the country's only oncologic referral center. Overall survival after 2 years was considerably high (74%) compared with data from African cancer registries, underlining the usefulness of radiotherapy. The survival was still lower than that of patients from higher-resource settings, probably because of the lack of brachytherapy. Therefore, brachytherapy for cervical cancer patients should be of high priority. Patients with earlier stages of disease had better outcome compared with those with later stages. Awareness and early detection programs are needed in the Ethiopian setting.

Introduction

Every year, almost 500,000 women worldwide are estimated to be newly diagnosed with cancer of the cervix uteri [1]. The majority of cases are found in developing countries; in Africa almost 60,000 women die of the disease each year [2]. In 2004, cervical cancer contributed to 3.4 million years of life lost (YLL) worldwide and was the greatest single cause of YLL from cancer in women from low-income countries [3]. This mainly reflects the absence of national cancer control programs, including vaccination, screening, and early detection, in most African countries. Cervical cancer accounts for 22% of cancer deaths in women aged 15–59 years, making it a symbol for global health disparity; it burdens young women from the poorest countries and the most disadvantaged populations [4, 5]. Cancer patients in sub-Saharan Africa tend to present with advanced disease [6]. Despite this, in 2010 radiotherapy was available in only 23 of 52 African countries—mostly in the northern and southern states of the continent. Brachytherapy was available in only 20 countries [7]. Only a small amount of epidemiological data on cervical cancer is currently available [8]; only five African cancer registries were included in the World Health

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Organization publication "Cancer Incidence in Five Continents, Volume IX" [9]. Variations in incidence are expected within countries between rural and urban settings [10], as well as between different regions [11]. Research on cancer in Africa is increasingly being facilitated through various initiatives (e.g., the Global Initiative for Cancer Registry Development in Low- and Middle-Income Countries and the African Organisation for Research and Training in Cancer) [12].

Ethiopia is the second most populated country in sub-Saharan Africa, with more than 42 million females [13]. Ethiopia is one of the least urbanized countries in the world, with only 16% of the population living in urban areas [14]. There are an estimated 7,000 new cases of cervical cancer in Ethiopia per year; nearly 5,000 people are estimated to die of the disease per year [15]. Public oncological treatment in Ethiopia, including radiotherapy, is limited to the Radiotherapy Center at Tikur Anbessa University Hospital, which is staffed by four radiation oncologists. Treatment options for patients with cervical cancer are radical hysterectomy (Wertheim operation) when in the early stages, at the Department of Gynaecology at Tikur Anbessa Hospital. External-beam radiation can be given combined with chemotherapy at the Radiotherapy Department. Brachytherapy is not available in Ethiopia. When attending the hospital, patients first have to register at the Radiotherapy Department for an appointment with the radiation oncologist. At this appointment, evaluation and planning of radiotherapy is performed by the radiation oncologist. Thereafter, patients receive an appointment to start radiotherapy. Because of huge patient loads, a considerable amount of time may pass between these appointments. Patients with acute bleeding receive priority for appointments for emergency radiation. Little is known about the outcome of cervical cancer patients who receive therapy in such settings with limited resources. Recent publications point toward the need for more epidemiological data on noncommunicable diseases, including cancer, for example from cohort studies [16, 17].

The primary aim of this study was to estimate the overall survival of women with cancer of the cervix uteri whose diagnosis and treatment by surgery and/or radiotherapy at the Radiotherapy Center Addis Ababa took place between September 10, 2008 and September 11, 2012.

Materials and Methods

Patients and Methods

Women with histologically verified cancer of the cervix uteri (International Classification of Disease-Oncology (ICD-O-3) codes C53.0–9) who were diagnosed and treated between September 10, 2008 and September 11, 2012 at the Radiotherapy Center at Tikur Anbessa Hospital in Addis Ababa, Ethiopia, were included in the study. Treatment consisted of radiotherapy and/or surgery. All patient characteristics, tumor characteristics, and information concerning therapy and outcome were extracted from the patients' files. Waiting time was calculated between the date of the first presentation at the hospital and start of radiotherapy. All patients with telephone numbers available were contacted by telephone. Information on the date of last contact and survival status was obtained by telephone from the patients or—in case of death—from relatives. If patients or relatives were not reached by telephone, the last date of personal contact was taken from the patients' files.

Staging

Tumors were classified according to the International Federation of Gynecology and Obstetrics (FIGO) staging system [18]. The FIGO stage was based on clinical examination by at least one of the four radiation oncologists from the Radiotherapy Center (by authors A.M., T.W., and A.A.) and was documented in the patients' files. The FIGO stage at first presentation to the hospital was used for further analysis. In cases of discrepancy between examinations, another radiation oncologist was consulted. In a few cases of additional radiologic or sonographic detection of hydronephrosis around the time of diagnosis, the FIGO stage was classified as stage IIIb; in cases of distant metastasis, the FIGO stage was classified as stage IVb (by authors U.M. and M.B.). Patients with lack of findings on routinely performed chest x-ray and abdominal ultrasound were considered "free of distant metastasis." The histological results were documented according to written notes from pathology reports.

Treatment Modalities

Patients with cervical cancer were referred from all over Ethiopia to Tikur Anbessa Hospital for radiotherapy. This hospital has one cobalt-60 teletherapy unit. Patients with early-stage disease residing in Addis Ababa were referred for surgery as well. The surgical treatment was radical hysterectomy with pelvic lymphadenectomy (Wertheim). This surgery was performed in cases of FIGO stages Ia, Ib, and IIa. Tikur Anbessa Hospital is the only hospital in Ethiopia regularly performing Wertheim surgery and the only facility administering combination radiochemotherapy. Patients with a FIGO stage lower than IIb and clear surgical margins and negative lymph nodes did not receive radiotherapy. Also, patients with renal failure did not receive radiotherapy.

Adjuvant, radical, and palliative radiotherapy were applied in two phases. In the first phase, opposing-field techniques (anterior-posterior/posterior-anterior) were used, and in the second phase, four-field box techniques were applied. Typically, opposing fields in the first phase were 20–22 by 20–22 cm in size and included the gross tumor volume and the pelvic lymph nodes (upper border: L5/S1, lower border: 2–3 cm below palpable tumor, lateral borders to include inguinal nodes). In the second-phase, boost series directed only at the gross tumor volume, the typical size of an anterior field in the four-field box technique was 12 by 14 cm.

Adjuvant radiotherapy was given to patients after surgery without clear surgical margins or with positive lymph nodes and/or parametrium involvement. The patients received 40 Gy in 20 fractions of 2.0 Gy within 4–5 weeks in the first phase. Depending on tumor response, adverse effects, and compliance of the patients, a boost dose of 20–26 Gy was applied in 10–13 fractions of 2.0 Gy within 2–3 weeks in the second phase. In cases of FIGO stage IIb or IIIa, as well as cases of FIGO stage less than IIb without surgery, primary radical radiotherapy was given. The patients received 46 Gy in 23 fractions of 2.0 Gy within 5–6 weeks in the first phase and 26 Gy in 13 fractions within 2–4 weeks in the second phase. Patients with FIGO stage IIIb or 4a without bilateral hydronephrosis or clinical fistula

were given palliative radiotherapy with a larger dose per fraction: 32 Gy in 8 fractions of 4.0 Gy within 4 weeks in the first phase followed by a second phase of 18 Gy (6 fractions of 3.0 Gy) or 12 Gy (4 fractions of 3.0 Gy) within 2–3 weeks. In cases of FIGO stage IVa or IIIb with bilateral hydronephrosis, stage IVa with clinical fistula, or FIGO stage IVb, the patients received two single fractions of 10 Gy each, and depending on response, performance status, and site of metastasis, they received additional radiotherapy or palliative chemotherapy.

The waiting time for application of single-fraction radiotherapy was short (1–2 days), and therefore this concept was also applied for FIGO stage I–II patients who were unable to stay in Addis Ababa for longer periods of time because of their socioeconomic background. This applied to 12% of patients with FIGO stage Ia–IIa and 15% of patients with FIGO stage IIb–IIIa. Hemostatic radiotherapy (12 Gy in 4 fractions) was administered independently of FIGO stage because of massive vaginal bleeding and decline in hematocrit. In curative concepts, chemotherapy was recommended simultaneous with curative radiotherapy or rarely neoadjuvant to surgery (cisplatin, 60 mg/m^2, 3–6 cycles). Palliative chemotherapy with cisplatin and 5-fluorouracil (50 mg/m^2, 6 cycles) was recommended to patients with FIGO stage IIIb–IVb. Because of the limited availability of the substances and the financial limitations of the patients, chemotherapy was not administered on a regular basis.

Statistical Analysis

The primary endpoint of this study was overall survival. Person time equaled the time from the date of pathologic diagnosis to death or to closing date for follow-up (August 7, 2013), whichever came first. Women were right-censored at the date of last contact before the closing date. The survival probabilities in months were estimated using the Kaplan-Meier method. The 95% confidence intervals at year 2 are shown. Kaplan-Meier estimates were compared using the log-rank test. Analyses were conducted using SPSS Statistics, version 19 (SPSS software, IBM Corp., Armonk, NY, http://www-01.ibm.com/software/analytics/spss/) and SAS (SAS Institute, Inc., Cary, NC, http://www.sas.com), version 9.3. The median follow-up time for surviving patients was 16.5 months (range, 0.1–53.0 months). In the first analysis, we assumed right censoring to be unrelated to the risk of distant metastasis. Worst-case analysis assumed that all patients who were not available for follow-up after 6 months had died.

Ethics

For this study, ethical approval was obtained from the Institutional Review Boards of Addis Ababa University School of Medicine and Martin Luther University Halle. The study was conducted without individual informed consent because the study relied on retrospective data collected as part of routine patient care.

Results

Description of the Study Population

Between September 9, 2008 and September 11, 2012, an estimated 2,300 patients with cancer of the cervix uteri were registered at the Radiotherapy Center. This includes 111 patients who received surgery for the cancer. Of those, 1,837 were seen by the radiation oncologist, and radiotherapy was planned. The estimated number of patients who received radiotherapy was 1,400. Of those, 1,012 patient files could be retrieved. An additional 47 patients who received only surgery for early-stage cervical cancer were included in the study. Note that an estimated 900 patients who registered never received any therapy (Fig. 1).

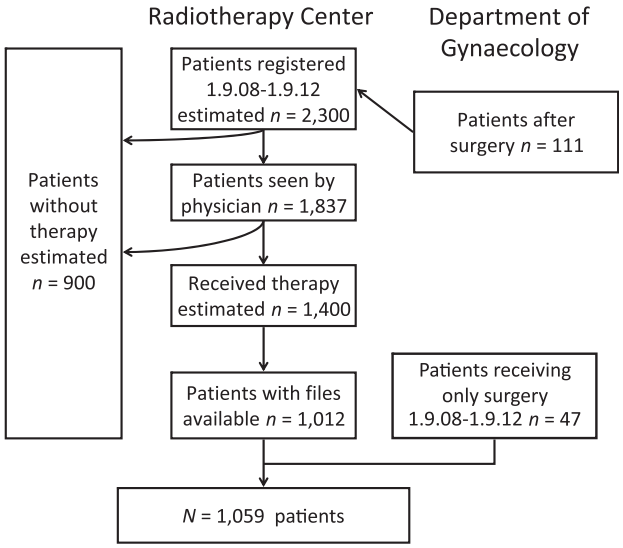


Figure 1. CONSORT diagram. Patients diagnosed with cancer of the uterine cervix included in this study are a subgroup of all who presented at the Radiotherapy Center or Department of Gynecology of Tikur Anbessa University Hospital, Addis Ababa.

Patient Characteristics

Most patients came from rural areas (56.5%). The largest group of patients were 40–49 years old (30.9%). The majority of patients (78.1%) were postmenopausal. The mean number of children was 6.0, with 10% and 90% percentiles of 2 and 10, respectively. Many women reported only one lifetime sexual partner (52.7%), as well as marriage before the age of 18 (83.9%). The proportion of women using contraceptives was 31.1%. A total of 9.4% were known to be HIV-positive. The Eastern Cooperative Oncology Group performance status 1 at first presentation was common (57.8%). The largest group of patients presented with FIGO stage IIb–IIIa (46.7%) and squamous cell carcinoma (93.4%) (Table 1).

An important piece of baseline information is change in FIGO stage between pathological diagnosis and the start of radiotherapy, during which time a considerable number of patients died while waiting for treatment. However, information about these patients was not available. Because of the huge patient load, the median waiting time was 1.8 months between first registration at the Radiotherapy Center and the first appointment with the radiation oncologist (10th and 90th percentiles were 0.2 and 5.2 months, respectively). The median waiting time between the appointment with the radiation oncologist and the start of radiotherapy was 0.2 months for emergency radiotherapy, 1.7 months for curative radiotherapy, and 2.3 months for palliative radiotherapy (supplemental online Fig. 1). The proportion of patients with advanced stage IIIb and above increased between the

Table 1. Basic demographic data of the 1,059 patients when first seen by a physician

Characteristics	Number	Proportion (%)
Total population	1,059	100
Place of origin		
Urban (10 biggest cities)	461	43.5
Only Addis Ababa	311	29.4
Rural	598	56.5
Age (years)		
<30	28	2.6
30–39	178	16.8
40–49	326	30.8
50–59	287	27.1
≥60	240	22.7
Menopausal status		
Premenopausal	221	20.9
Postmenopausal	827	78.1
Unknown	11	1.0
Marriage		
Early (≤18 years)	888	83.9
After age 18	67	6.3
Unmarried	10	0.9
Unknown	94	8.9
Parity (mean and standard deviation; information available for 97.8% patients)	5.99 ± 3.137	
Sexual partners		
None	2	0.2
One	558	52.7
Few (2–3)	157	14.8
Multiple (>3)	233	22.0
Unknown	109	10.3
Contraceptives		
Hormonal (pill, injectable, implant)	293	27.7
Nonhormonal (IUD, condoms, tubal ligation)	17	1.6
Combined	19	1.8
None	677	63.9
Unknown	53	5.0
HIV status		
Positive	100	9.4
Negative/unknown/not screened	959	90.6
First ECOG		
Fully active (ECOG 0)	5	0.5
Lightly restricted (ECOG 1)	612	57.8
Unable to work (ECOG 2)	315	29.7
Limited self-care >50% in bed (ECOG 3)	117	11.0
No self-care, bedbound (ECOG 4)	10	0.9
Stage (FIGO)		
Ia–IIa	174	16.4
IIb–IIIa	495	46.7
IIIb–IVa	355	33.5
IVb	7	0.7
Recurrence	28	2.7
Histology		
Squamous	989	93.4
Keratinizing	302	28.5
Nonkeratinizing	348	32.9
Not specified	339	32.0
Adenocarcinoma	54	5.1
Adenosquamous carcinoma	11	1.0
Small cell	3	0.3
Other/unspecified/unknown	2	0.2
Grade		
Well differentiated	76	7.2
Moderately differentiated	94	8.9
Poorly differentiated	59	5.5
Undifferentiated	7	0.7
Not done	823	77.7

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

appointment with the radiation oncologist (44.2%) and the start of radiotherapy (68.3%) (Fig. 2).

Treatment Modalities

The majority of patients received radiotherapy; only 4.4% received surgery only for early stages of the disease. Out of 158 patients receiving surgery, the majority (n = 143; 70.8%) received radical hysterectomy, six received simple hysterectomy, and nine surgeries were of unknown extent. Palliative radiotherapy was administered to almost half of the patients. Because of the lack of finances or availability of the drugs, only 96 patients received simultaneous radiochemotherapy (Table 2).

Survival

Within the whole cohort, a total of 212 deaths were registered. Another 37 patients were reported dead at the time of telephone interview, but the date of death remained unknown. Therefore, these patients were entered as alive and censored at the time of last personal appointment documented in the files. A total of 378 patients were lost to follow-up; therefore a worst-case analysis was performed (see Materials and Methods). The estimated overall survival is shown for the total patient cohort. The estimated 1- and 2-year survival probabilities were 90.4% and 73.6%, respectively (note at the end of year 3, the number of patients under observation declined to 8). In the worst-case analysis the estimated 2-year overall survival declined to 45.40% (Fig. 3). The median survival time was 40.6 months, declining to 21.5 months for the worst-case analysis. The estimated 2-year overall survival was most favorable for patients with FIGO stage Ia–IIa disease at the time of first presentation (84.8%, or worst-case 66.7%). Patients with FIGO stage IIb–IIIa had lower overall survival probabilities (79.5%, or worst-case 53.1%), and patients with FIGO stage IIIb–IVa the lowest (55.8%, or worst-case 25.3%) estimated

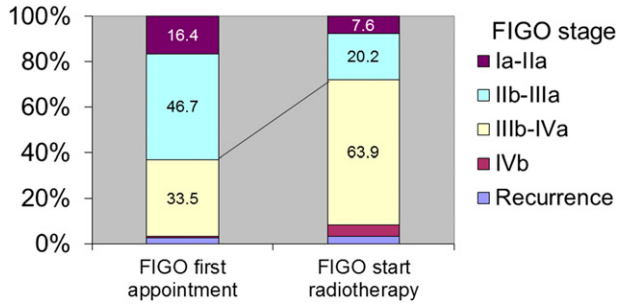


Figure 2. Changes in FIGO stage during waiting time. FIGO stage was evaluated at the first visit to the radiation oncologist at the Radiotherapy Department and then at the start of radiotherapy. The proportion of higher FIGO stages in the cohort increased during this period.

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

overall survival probabilities after 2 years. There were only a few patients with FIGO stage IVb disease ($n = 7$). Twenty-eight patients experienced recurrence. These cases together had an estimated 2-year overall survival probability of 54.6%, or worst-case 32.7%. Those patients represent a heterogeneous group with a rather unfavorable estimated survival probability (Fig. 4). Comparison of the FIGO stages showed relevant differences in survival probability between stages ($p < .001$). Comparing patients' outcome according to the dose of radiation showed better outcome for higher doses: 2-year survival probabilities were 80.8%, 72.3%, and 46.6% for 52 Gy and above, 32–50 Gy, and 4–30 Gy, respectively (supplemental online Fig. 2). Outcome by 2-year survival probabilities according to intention of treatment was best in the post-operative adjuvant situation (90.6%), radical radiotherapy (79.9%), followed by palliative radiotherapy (68.6%), and single fraction approach (50.3%) (Fig. 5).

Discussion

This is the first study from Ethiopia and also sub-Saharan Africa to report on the outcome of a large cohort of patients who received oncologic therapy for cancer of the cervix uteri. With a median follow-up time of 16.5 months (for surviving patients), the overall survival was 90.4% and 73.6% at 1 and 2 years, respectively. In total, 55.8% and 34.6% of the patients presented with stages IIb–IIIa and stage IIIb, respectively. We found extremely long waiting times until the start of radiotherapy (median 3.8 months) leading to even higher proportions of patients with late-stage disease by the time radiotherapy was started.

Cancer survival data from Africa are mainly based on cohorts from national or regional population-based registries. Therefore, we discuss our data with respect to these published results. It should be noted that the registry cohorts aim at including all cases irrespective of stage of disease or whether treatment was received. Our cohort lacks late-stage patients who died before the start of therapy and poor patients unable to pay for therapy ($n = 900$; Fig. 1). Therefore, because of the nature of our cohort, survival was expected to be more favorable compared with population-based data.

Table 2. Treatment modalities

Characteristics ($N = 1,059$ patients)	Number	Proportion (%)
Surgery only	47	4.4
Surgery and radiotherapy	111	10.4
Radiotherapy only	901	85.1
Radiotherapy	1,012	
Curative (60–72 Gy)	278	27.5
Palliative (44–50 Gy or hemostatic)	459	45.3
Palliative single fraction (10–38 Gy)	275	27.2
Chemotherapy		
Neoadjuvant to surgery (no radiotherapy)	2	0.2
Neoadjuvant to surgery followed by radiotherapy	26	2.4
Concurrent to curative radiotherapy	97	9.1
Palliative chemotherapy after palliative radiotherapy	54	5.1
For other neoplasia	2	0.2
No chemotherapy	878	82.9

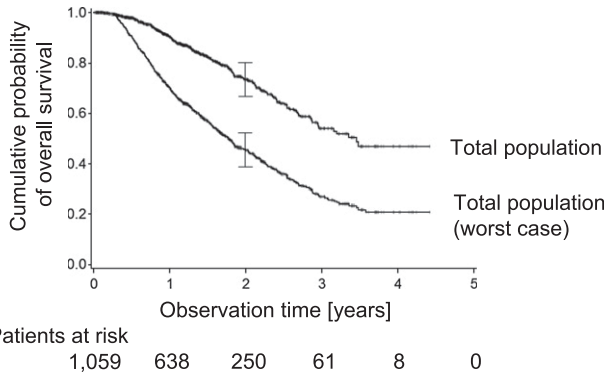
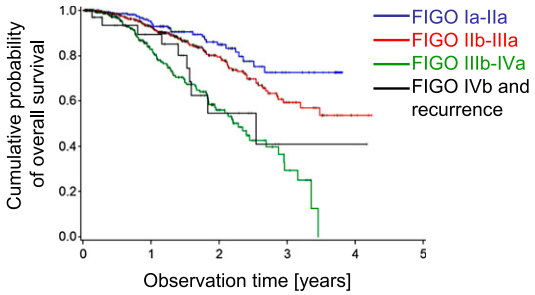


Figure 3. Cumulative overall survival probability. The uncorrected estimated overall survival time of the total cohort is shown (upper curve). The worst-case scenario assumes that patients who did not come to appointments for more than 6 months had died after the last appointment (lower curve).

Data from the population-based cancer registry of Kampala/Uganda show a 5-year age-standardized survival of 19% in 1993–1997 [19]. The Harare/Zimbabwe cancer registry ($n = 284$, half treated with radiotherapy) found a 3-year overall survival of 44.2% [20]. Sankaranarayanan et al. [21] report 5-year overall survival rates of 22% and 13% in the Gambia and Uganda, respectively. In our study, we found a 2-year overall survival of 74%, which is higher than the data from Zimbabwe and considerably better than the data from the Gambia and Uganda. This higher survival may point to a positive radiotherapy treatment effect beyond the lack of late-stage patients in our cohort.

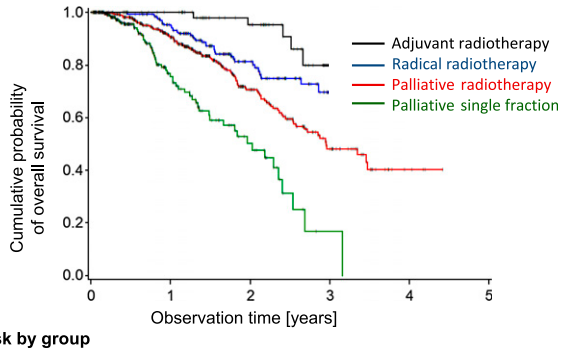
Looking at high-income countries, Petereit et al. [22] reviewed treatment results in 5,619 patients receiving external beam radiotherapy followed by high-dose brachytherapy as reported in original publications between 1985 and 1997. The FIGO stages in their cohort were comparable to our cohort. The



Patients at risk					
FIGO Ia-IIa	175	129	65	16	3
FIGO IIb-IIIa	494	347	134	36	4
FIGO IIIb-IVa	355	141	44	8	0
FIGO IVb+rec.	35	21	7	1	1

Figure 4. The estimated cumulative overall survival time according to FIGO stage at the first presentation to the radiation oncologist is shown. Group 1 is FIGO stage Ia–IIa, group 2 is FIGO stage IIb–IIIa, group 3 is FIGO stage IIIb–IVa, and group 4 is FIGO stage IVb and recurrences.

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; rec., recurrences.



n at risk by group					
Adjuvant RT	66	58	33	8	1
Radical RT	212	170	69	17	3
Palliative RT	459	303	104	34	4
Single fraction	275	58	16	0	0

Figure 5. The estimated cumulative overall survival time according to intent of radiation is shown.

Abbreviation: RT, radiotherapy.

overall 5-year survival probabilities were higher than our findings: 85%, 68%, and 47% for FIGO stages I, II, and III, respectively [22]. The lack of brachytherapy in our cohort may explain the lower survival probabilities observed.

Looking at medium income countries, overall 5-year survival probabilities from Asia and Central America (population-based registries, tumor stages unknown) were higher than our cohort: for example, China 82%, India, 46% and Costa Rica, 53% [21]. The African American population from the SEER database showed an overall 5-year survival of 58% [23]. The lack of early detection activities, as well as the lack of therapeutic options in our cohort, may explain the lower survival probabilities we observed.

Late stage at presentation is a major prognostic factor for decreased survival. In our cohort, 34.2% of the patients were diagnosed at FIGO stage IIIb and above. This is comparable with data reported from Cape Town/South Africa, where screening was not available between 1984 and 2000 [24]. As an example of a country with high screening activity, data from Germany showed that 66% and 22% of the women presented with T1 and T2 tumors, respectively [25]. Because of the lack of screening opportunities in Ethiopia, patients usually present late with symptomatic disease.

Prevention, screening, and early detection have been proven useful also in low-resource settings. In Africa, screening with visual inspection and acetic acid combined with immediate cryotherapy of suspicious lesions has been implemented regionally. Recently, the role of human papillomavirus (HPV) testing in screening programs is under discussion. Additionally, HPV vaccination has become a possible option for primary prevention [26–29]. In Ethiopia, there is little awareness of HPV and CC within society, and symptoms of vaginal bleeding are socially stigmatized. The benefits of modern therapy are still perceived as low [30]. Vaccination, screening, or early detection are not available for most of the population [15]. Studies from different African countries (e.g., Nigeria and Uganda) show positive uptake of screening service after community-based advocacy [31, 32]. Rwanda has now become the first country in Africa to implement a nationwide program, including vaccination, early detection, and screening [33]. These options could eventually change the burden of cervical cancer disease in Africa [4, 34].

As expected, we found a high proportion of HIV-positive patients (9.4%). The true rate may have been even higher, because general screening of all new patients was conducted only in years 2–4 of the study. The Ethiopia Demographic and Health Survey from 2010 reported that 1.5% of women aged 15–49 were HIV-positive [14]. Ongoing efforts in Ethiopia to screen HIV-positive women for cervical cancer seem justified [15].

There are certain factors that limit our results. First, there is no clinical information on patients who registered but never saw a physician (estimated $n = 463$). Economic reasons, logistic reasons, and progression of the disease are possible explanations. Other patients (estimated $n = 437$) saw a physician but never started therapy—the relevant files could not be retrieved. We assume that a number of very advanced cases were not included in this study, leading to more favorable characteristics than in the overall cohort of patients presenting at the referral hospital. Second, radiotherapy did not include the application of brachytherapy. This is known to be a suboptimal standard of treatment. Because half of all radiotherapy departments in Africa are not able to offer brachytherapy, we still consider these findings of interest for countries with limited resources. Third, we were unable to retrieve almost 400 files (27%) belonging to patients who received therapy. The files are handwritten and manually stored, and names also vary in spelling. Misplacing is common. We are not aware of any other reason for missing files, and therefore we do not suspect any associated selection bias. Despite these limitations, our study is the first to thoroughly characterize and follow >1,000 patients in the clinical setting and therefore adds information about cervical cancer in Africa to the literature.

Conclusion

In this study, we present a description and follow-up of 1,059 patients diagnosed with cancer of the cervix uteri between September 2008 and 2012 at Addis Ababa Radiotherapy Center. We found a relatively high estimated 2-year overall survival of

73.6% (declining to 45.5% in the worst-case analysis). This survival is higher than previously reported from African cancer registries. It probably reflects a positive effect of the treatment, as well as selection bias through lack of untreated late-stage patients in our hospital cohort. The survival is lower than that of treated patients in high-income settings, which probably reflects the lack of brachytherapy in Addis Ababa. Stage at presentation in Addis Ababa is late, and the disease progresses during waiting times. Later stages showed lower survival probabilities compared with earlier stages, and higher radiation doses showed higher survival probabilities compared with lower doses. There is an urgent need for increased awareness, primary prevention by vaccination, and early detection programs to increase early stages at presentation. To further improve survival, radiotherapy, including brachytherapy, should be made available sooner.

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Disclosures

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/ inventor/patent holder; (SAB) Scientific advisory board

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See http://www.TheOncologist.com for supplemental material available online.

For Further Reading:

Julie S. Townsend, Analía Romina Stormo, Katherine B. Roland et al. Current Cervical Cancer Screening Knowledge, Awareness, and Practices Among U.S. Affiliated Pacific Island Providers: Opportunities and Challenges. ***The Oncologist*** 2014; 19:383–393.

Implications for Practice:

The U.S. Affiliated Pacific Island Jurisdictions (USAPIJ) are located in a geographically disparate region with a high burden of cervical cancer. Although cervical cancer screening providers in the USAPIJ stated that screening is a priority in clinical practice, costs associated with screening and varying levels of support for alternative screening tests pose barriers to screening throughout the USAPIJ. Use of alternative screening tests and routine monitoring and quality assurance to ensure all eligible women are reached may be needed to reduce the cervical cancer burden in the USAPIJ and to ensure effective use of limited resources.

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The prevalence of estrogen receptor-negative breast cancer in Ethiopia

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Abstract

Background: In contrast with breast cancers (BCs) in other parts of the world, most previous studies reported that the majority of BCs in sub-Saharan Africa are estrogen-receptor (ER) negative. However, a recent study using the US SEER database showed that the proportion of ER-negative BC is comparable between US-born blacks and West-African born blacks but substantially lower in East African-born blacks, with over 74% of patients Ethiopians or Eritreans. In this paper, we provide the first report on the proportion of ER-negative BC in Ethiopia, and the relation to progesterone-receptor (PgR) status.

Methods: We analysed 352 female patients with ER results available out of 1208 consecutive female BC patients treated at Addis Ababa-University Hospital, Ethiopia, from June 2005 through December 2010. The influences of age, stage, and histology on the probability of ER-negative tumours were assessed by a log-linear regression model.

Results: Of the 352 patients, only 35% were ER-negative. The proportion of ER-negative tumours decreased with advancing age at diagnosis and was not affected by histology or stage. For age, the proportion decreased by 6% for each additional 5 years (stage-adjusted prevalence ratio PR = 0.94, 95% CI: 0.89–1.00). About 31% were ER- and PgR-negative, and 69% were ER- and/or PgR-positive.

Conclusions: Contrary to most previous reports in other parts of sub-Saharan Africa, the majority of patients in Ethiopia are ER-positive rather than ER-negative. These findings are in line with low proportions of ER-negative BCs from East African immigrants within the SEER database, and they have clinical implications for management of BC patients in Ethiopia and other parts of sub-Saharan Africa where ER-status is not ascertained as part of routine management of the disease. Since the majority of patients showed ER-positive BC, Tamoxifen-therapy should be given to all patients even with unknown ER status.

Keywords: Breast neoplasms, Africa, Ethiopia, Prognostic factors

Background

Knowledge of the estrogen-receptor (ER) status of breast cancer (BC) is essential in making the decision to treat women with Tamoxifen. Population-based estimates of the distribution of the receptor status of BCs can aid treatment decisions, even among women in whom the individual ER status has not been assessed. Often breast tumours in the African setting are described as being aggressive with negative ER status. Results from East Africa showed 76% of the patients in Kenya and more than two thirds of the patients in Tanzania and Uganda were ER-negative [1-3]. The majority of studies from West Africa showed more than half of the patients were ER-negative: in Nigeria and Senegal, 76% [4]; in Ghana, 76% [5], 75% [6] and 53% [7] and in Mali, 61% [8]. One study from Nigeria, one from Uganda, one from Ghana and one large study from South Africa showed lower proportions of ER-negative tumors (35%, 40%, 24% and 37%, respectively) [9-12] (Table 1).

The discrepancies in the proportion of ER-negative tumours in Africa are thought to reflect the selection

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Table 1 Selection of published results of breast cancer hormone receptor-results (from PubMed terms "AFRICA" and "BREAST CANCER" and "HORMONE RECEPTOR" or "ESTROGEN RECEPTOR" searched June 5, 2014)

	Total (n)	Year of specimen collection	% of negative estrogen receptor status
East Africa			
Kenia [1]	120	2001–2007	76
Tanzania [2]	60	1995–1997	67
Uganda [3]	65	1993–2002	65
West Africa			
Nigeria/Senegal [4]	507	2004–2005	76
Ghana [5]	75	2007–2008	76
Ghana [6]	100	2006–2011	75
Ghana [10]	51	2007-2010	76
Mali [8]	114	2008–2011	61
Uganda [11]	45	2000-2004	60
Ghana [7]	68	2004–2009	53
Nigeria [9]	133	1996–2007	35
Southern Africa			
South African black population [12]	957	2006–2012	37

bias of cases and methodological problems associated with laboratory procedures, including degradation of tissue during storage. Also low sensitivity of ER-testing and false negative cases can contribute. Possible regional differences in populations may account for the heterogeneous results involving these tumour biological characteristics but this is questioned by studies showing large differences in the ER-positive proportion within the same population [10]. A recent publication by Jemal *et al.* showed that U.S. immigrants from West Africa with BC had high percentages of ER-negative disease (39.5%). U.S. immigrants with BC from East Africa, mainly Ethiopia, had ER-negative BC in only 25.3% similar to U.S.-born whites with BC [13]. To investigate ER-negative proportions of BC patients, we evaluated for the first time patient and tumour characteristics of a case series of female patients diagnosed with invasive BC from Addis Ababa, Ethiopia.

Methods

Ethical approval for this study was obtained from the Institutional Review Boards of Addis Ababa University Medical Faculty. The study was conducted without individual informed consent because it relied on retrospective data collected as part of routine patient care. The study was a hospital-based cohort study at the radiotherapy centre of Addis Ababa University Hospital. Women with a histologically verified primary diagnosis of invasive BC between 1 June 2005 and 31 May 2010 who consulted the radiotherapy department at Tikur Anbessa Hospital Addis Ababa were included. The files of BC patients were retrieved manually. All demographic, clinical and pathological characteristics were documented from patients' files containing physicians' notes, pathology reports and referral letters.

According to international coding standards for cancer registries [14], the date of incidence was defined as the first consultation at a hospital for the cancer in question or later diagnostic confirmation (e.g. diagnosis by a physician, pathology, date of death). Information about tumour size (T) and nodal status (N) was used to derive the AICC/UICC stage [15]. All staging information mentioned within the first three months after primary pathological information was used for TNM staging [16]. In the case of a clinical T4 description, this was given priority over any pathological Tx. In case of neoadjuvant chemotherapy before the operation, clinical T assessed before chemotherapy was used for the T-stage. TNM classification recommends the removal of at least six lymph nodes (LN) of the axilla. This number of 6 LN was not always described in the pathology report. Therefore, we decided to classify N1 if >50% of the removed nodes were positive. In cases of 4–9 or 10+ positive nodes, we coded N2 or N3. Otherwise, Nx was documented (in line with the European Network of Cancer Registries recommendations [17]). M-stage: The presence of radiologically confirmed distant metastasis at diagnosis was considered to be M1.

In general, diagnosis of BC was obtained by fine-needle aspiration cytology (FNAC) or by surgical biopsy. Early cases were usually operated and therefore tumour material for histology was available. More advanced, inoperable cases or recurrences were usually diagnosed by FNAC only. Therefore, some patients had tumor

material for histology, and some only had cytologic material by FNAC available for ER determination and grading. Estrogen receptor staining was introduced in a prospective standardized manner within the independent Ethiopian BC project separately funded and initiated by AstraZenaca Ltd., England, facilitated by the Axios Foundation, France, 2005–2010. Immunohistochemistry was done soon after the specimen were obtained using the estrogen antibody ER 6 F11 and progesterone antibody PGR 312 with the Menarini detection kit according to the standard protocol (A. Menarini diagnostics International®, Firenze, Italy). Evaluation of the staining was done by experienced pathologists in the department according to guidelines assessing any positive stained cell (>1%) as positive ER status [18].

We estimated the percentage (hereafter referred to as "prevalence") of ER status within the total of ER-stained tumours and among subgroups of clinical importance. To assess the influence of age on the prevalence of ER-negative findings, we estimated prevalence ratios (PR) and corresponding 95% confidence intervals by using a log-linear regression model. Analyses were done using SAS® statistical software (SAS Inc., Cary, NC, USA), Version 9.3.

Results

The largest proportion of the study population of 1208 female patients was between 30–39 years old (35%). The proportion of patients from Addis Ababa (46%) was slightly higher than the proportion from non-Addis Ababa; the largest proportion of patients presented at stage 3 (36%), mostly without distant metastases at diagnosis (82%). The majority had ductal histology (78%). We compared these characteristics between the total population of 1208 patients and the subgroup of 352 patients with available ER results. The distribution of place of origin, menopausal status, histology and adjuvant therapy was similar. Patients with ER results available were more often under 30 or over 60 years, and also tended to have a higher stage at diagnosis than patients with ER results not available. Due to the preferred procedure of staining FNAC to determine ER, patients with ER results available had more often FNAC done for their pathological diagnosis (Table 2).

Within the subgroup of patients with ER results available, 34.7% (95% CI 28.9–38.8%) had ER-negative findings. The prevalence of ER-negative findings was associated with patients age. Based on a log-linear regression model, the estimated stage-adjusted prevalence of ER-negative findings decreased for each additional 5 years of age by 6% (PR = 0.94, 95% CI: 0.89–1.00), note the CI was close to 1.

Progesterone receptor was positive in 72% (162/224) of ER-positive tumours and 12% (14/120) of ER-negative tumours. None of the other patient characteristics, including place of origin that was not Addis Ababa, stage and histology, was associated with the prevalence of ER-negative results (Table 3, adjusted risk ratios). Results from the FNAC specimen as compared to the tumour specimen had a lower age- and stage-adjusted prevalence-ratio for ER negativity (PR = 0.71; 95% CI: 0.51–0.98).

Table 2 Clinical and pathological characteristics of the study population

Parameter	ER available: N (column%)	ER not available: N (column%)
Total population n = 1213	352 (100.0)	861 (100.0)
Place of origin		
Addis Ababa	183 (52.0)	405 (47.0)
Non-Addis Ababa	140 (39.8)	375 (43.6)
unknown	29 (8.2)	81 (9.4)
Age (years)		
<30	56 (15.9)	106 (12.3)
30–39	114 (32.4)	331 (38.4)
40–49	83 (23.6)	231 (26.8)
50–59	53 (15.1)	139 (16.1)
≥60	46 (13.1)	54 (6.3)
Menopausal status		
Premenopausal	145 (41.2)	345 (40.1)
Postmenopausal	155 (44.0)	374 (43.4)
Unknown status	52 (14.8)	142 (16.5)
Stage (UICC)		
1 and 2	35 (9.0)	153 (17.8)
3	168 (47.7)	288 (33.4)
4	71 (20.2)	72 (8.4)
Unknown	78 (22.2)	348 (40.4)
Distant Metastasis		
No (M0)	236 (67.0)	666 (77.4)
Yes (M1)	116 (33.0)	195 (22.6)
Histology		
Ductal	265 (75.3)	681 (79.1)
Lobular	20 (5.7)	39 (4.5)
other/unspecified	67 (19.0)	141 (16.4)
Patho-specimen for diagnosis		
FNAC[+]	127 (36.1)	27 (3.1)
Tumour specimen	193 (54.8)	659 (77.0)
unknown	32 (9.1)	174 (20.2)
Basis of hormone receptor diagnosis		
Primary operation	174 (49.4)	Not applicable
Recurrence	106 (30.1)	
unknown	72 (20.5)	

[+]FNAC – fine needle aspiration cytology.

Table 3 ER results among different groups of patients

Parameter	ER: N (%) 352 stained tumours			
	Positive (% in row or mean and standard deviation)	Negative (% in row or mean and standard deviation)	ER-negative vs. ER-positive crude RR (95% CI)	ER-negative vs. ER-positive adjusted* RR (95% CI)
Total population n = 352	230 (65.3)	122 (34.7)		
Age [years] (mean and standard deviation)	43.0 (13.7)	40.1 (12.6)	Increase 5 yrs 1.02 (0.98–1.01)	Increase 5 yrs 0.94 (0.89–1.00)
Tumour size [cm] (mean and standard deviation; n = 168 results available)	5.47 (3.3)	6.06 (3.3)	Increase 1 cm 1.03 (0.98–1.08)	Increase 1 cm 1.03 (0.97–1.08)
Place of origin				
Addis Ababa	123 (67.2)	60 (32.8)	Reference	Reference
Non-Addis Ababa	89 (63.6)	51 (36.4)	1.11 (0.82–1.50)	1.03 (0.76–1.41)
Unknown	18 (62.1)	11 (37.9)	1.16 (0.69–1.93)	1.10 (0.66–1.82)
Menopausal status				
Premenopausal	89 (61.4)	56 (38.6)	1.17 (0.87–1.59)	0.81 (0.54–1.23)
Postmenopausal	104 (67.1)	51 (32.9)	Reference	Reference
unknown	37 (71.2)	15 (28.8)	0.88 (0.54–1.42)	0.62 (0.36–1.07)
Stage (UICC)				
1 and 2	24 (68.6)	11 (31.4)	0.89 (0.53–1.52)	0.92 (0.54–1.56)
3	109 (64.9)	59 (35.1)	Reference	Reference
4	48 (67.6)	23 (32.4)	0.92 (0.62–1.37)	0.96 (0.65–1.42)
Unknown	49 (62.8)	29 (37.2)	1.06 (0.74–1.51)	1.06 (0.75–1.51)
Histology				
Ductal	171 (64.5)	94 (35.5)	Reference	Reference
Lobular	12 (60.0)	8 (40.0)	1.13 (0.64–1.98)	1.05 (0.60–1.85)
Other/unspecified	47 (70.2)	20 (29.8)	0.84 (0.56–1.26)	0.83 (0.56–1.24)
Progesterone receptor				
Positive	162 (92.0)	14 (8.0)	Reference	Reference
Negative	62 (36.9)	106 (63.1)	7.93 (4.74–13.28)	7.81 (4.66–13.09)
Unknown	6 (75.0)	2 (25.0)	3.14 (0.86–11.55)	3.47 (0.94–12.78)
Basis of hormone receptor diagnosis				
Primary operation	117 (67.2)	57 (32.8)	Reference	Reference
Recurrence	62 (58.5)	44 (41.5)	1.12 (0.96–1.31)	1.08 (0.91–1.27)
Unknown basis	51 (70.8)	21 (29.2)	0.89 (0.59–1.35)	0.87 (0.58–1.33)
Patho-specimen for diagnosis				
FNAC^{+}	92 (72.4)	35 (27.6)	0.67 (0.48–0.94)	0.71 (0.51–0.98)
Tumour specimen	114 (59.1)	79 (40.9)	Reference	Reference
Unknown	24 (75.0)	8 (25.0)	0.61 (0.33–1.14)	0.61 (0.33–1.16)

$^{+}$FNAC – fine needle aspiration cytology.
*Risk ratios were adjusted for age and stage, unless this was the variable of interest, RR for age was not adjusted.

Discussion

In our study, the tumour biology of female Ethiopian BC patients was favourable: only a small proportion, 34.7%, of patients had ER-negative BC (results available, n = 352). Older age predicted lower proportions of ER negativity (decrease in 5 years: 6.4%). All other patient characteristics, especially advanced stage, histology and ER results from local recurrence, did not predict ER negativity. Results from FNAC were less often ER-negative than results from tumour specimens.

Our study is in line with the findings of Jemal *et al.* [13], showing that U.S. immigrants from East Africa have a low proportion of ER-negative breast tumours, and studies from Nigeria, Ghana, Uganda and from South Africa that found <35% of ER negativity in BC patients from Africa [9-12]. The majority of studies on

tumour biology in Africa found large proportions of ER-negative tumours. Reasons for these findings might be true differences in the population due to environmental and genetic factors. However, it cannot be ruled out that these findings might also reflect bias due to lack of standardized staining and reading procedures, possible antigen degradation of archived material, and patient selection.

A limitation of our study is we only tested ER status on 29% of all the cases. However this group did not differ much from the total cohort of 1208 cases in clinical and pathological characteristics. Another limitation of our study is using results from FNAC staining among 36.1% of the cases instead of the gold standard histologic staining. In the cohort, FNAC showed a lower proportion of ER-negative results compared to the gold standard of histologic staining. Even though FNAC is not the gold standard, we believe FNAC staining does accurately reflect the immunohistochemical results for the tumour as comparative studies have shown [19-21]. Since FNAC is done more often in advanced cancer cases, the group with available ER results has a higher proportion of advanced stage patients, i.e. stage 4 (20.2% compared to 8.4%). Additionally, ER was sometimes stained on material from local recurrence. Jabbour et al. in their review article describe a 20% variation of ER expression between local recurrence and primary tumour, rather than switching from ER-positive to ER-negative expression in recurrences. Also, more advanced stages rather tend to be receptor-negative more frequently [22]. Therefore, our patient cohort would be expected to have high false ER-negative expression due to some results originating from recurrence material compared to the original primary tumours. Since our findings show a low ER-negative proportion, this proportion would even be lower in the primary and early stage tumours often described in studies from the Western world. Therefore, our results would even overestimate the proportion of ER-negative findings.

Conclusion

Our study showed that the proportion of ER-negative BC is low in Ethiopia (35%) using 352 BC cases with results available from a large consecutive cohort. These findings are in line with low proportions previously reported from East-Africa-born US-patients and other studies from Africa [10,11,13]. In case of low proportions of ER-positive cases in the routine, suspicion should be raised and a reference laboratory consulted. Hormone receptor staining is not often available in Ethiopia due to limited resources. From our findings, we conclude that patients with unknown receptor status are more likely to be ER-positive and therefore should be treated with Tamoxifen. This is especially true for older patients with lower chances of ER-negative disease.

Abbreviations

BC: Breast cancer; ER: Estrogen receptor; FNAC: Fine-needle aspiration cytology; PgR: Progesterone receptor.

Competing interests

The authors declared that they have no competing interests.

Authors' contributions

EJK made substantial contributions to the concept and design of the study, analysed and interpreted the data and has drafted the manuscript; AM made substantial contributions to the concept and design of the study, acquired clinical data and has helped drafting the manuscript; AA has acquired clinical data and critically revised the manuscript; TW has acquired clinical data and critically revised the manuscript; AJ made substantial contributions to the concept and critically revised the manuscript; MV has interpreted the data and critically revised the manuscript; EK has acquired clinical data and critically revised the manuscript; AR made substantial contributions to the concept and design of the study and critically revised the manuscript; SB has acquired clinical data and critically revised the manuscript; CT has interpreted the data and critically revised the manuscript; AS has interpreted the data and critically revised the manuscript; TG has acquired clinical data and critically revised the manuscript; PT made substantial contributions to the concept and design of the study, analysed and interpreted the data and critically revised the manuscript; BY has acquired clinical data, made substantial contributions to the concept and design of the study, analysed and interpreted the data and has drafted the manuscript; All authors have given final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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A Review on Breast Cancer Care in Africa

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Keywords

Africa · Breast neoplasms · Outcome · Therapy · Review

Summary

Background: The global incidence of breast cancer (BC) is rising, especially in low- and middle-income countries. The purpose of this review is to summarize existing publications on BC care in Africa. **Patients and Methods:** A systematic search in MEDLINE and smaller databases was carried out to identify African studies on BC treatment, and an additional PubMed search was performed for relevant topics on BC care. **Results:** A total of 219 publications, mainly from North and West Africa, were found by systematic search. We also selected articles on BC epidemiology, risk factors, clinical presentation, and cancer control in Africa. **Conclusions:** Publications on BC treatment are mostly from hospital case series. Evidence on treatment from prospective randomized trials that address the specific characteristics of African patients is lacking. The epidemiologic data shows rising incidences in Africa. The prevalence of risk factors is changing by age group, geographic region, and over time. The clinical picture of BC differs from that of Western countries due to the high proportion of young patients (on account of the African population with a high proportion of young people) and late presentation. Global collaborative efforts are needed to address the rising need for improved BC care in Africa.

Introduction

Non-communicable diseases, including breast cancer (BC), in Africa have been gaining more attention recently since improvements are seen in the management against infectious diseases, poor maternal health, and malnutrition. These days, non-communicable diseases are responsible for more than 60% of deaths around the world, with more than 80% of them occurring in low- and middle-income countries. More than 20% of these deaths from non-communicable diseases are cancer-related deaths [1].

BC has the highest incidence rate of all cancers in women worldwide (1.67 million) and accounts for over 500,000 deaths annually [2]. It has been said that African patients present late with aggressive tumors and face a lack of therapeutic options, resulting in short survival duration. Data on survival obtained from cancer registries in The Gambia and Uganda in the early years of this century reported an age-standardized 5-year relative survival between only 12 and 46% [3]. A comparison between West Africans, African Americans, and Caucasian Americans revealed higher proportions of high-grade, early-onset and estrogen receptor-negative cases in African patients [4].

Since the high-level meeting of the United Nations has focused attention on non-communicable diseases (chronic pulmonary and cardiovascular diseases, diabetes, and cancer) in 2011 [5], national cancer control programs have been developed and implemented. Several African first ladies have put the fight against female cancer (BC and cervical cancer) at the top of the national agenda [6]. This has encouraged clinicians and researchers in various countries to improve activities and to publish evidence available on the topic. Considering the huge diversity of the African continent in terms of ethnicities and genetic background, socio-economic development and health system status, culture and behavior, and many other areas, it is difficult to talk about BC in Africa in general. We used geographical divisions (West, North, South, East, and Central Af-

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Table 1. Publications according to years and regions, with the population in 2012 indicated

Years	Total	North Africa, 207 million		West Africa, 320 million		East Africa, 352 million		Central Africa, 133 million		Southern Africa, 58 million		Regional	
2010–2014	72	*33*[a]	*45.8%*	21	29.2%	8	11.1%	4	5.6%	3	4.2%	3	4.2%
2005–2009	54	20	37.0%	*22*	*40.7%*	6	11.1%			6	11.1%		
2000–2004	35	*14*	*40.0%*	10	28.6%	2	5.7%			9	25.7%		
1995–1999	15	3	20.0%	2	13.3%	1	6.7%	1	6.7%	*8*	*53.3%*		
< 1995	43	5	11.6%	*16*	*37.2%*	2	4.7%	1	2.3%	*16*	*37.2%*	3	7.0%
Total	219	*75*	*34.2%*	71	32.4%	19	8.7%	6	2.7%	42	19.2%	6	2.7%

[a]Countries with the highest numbers during the time period indicated in italics.

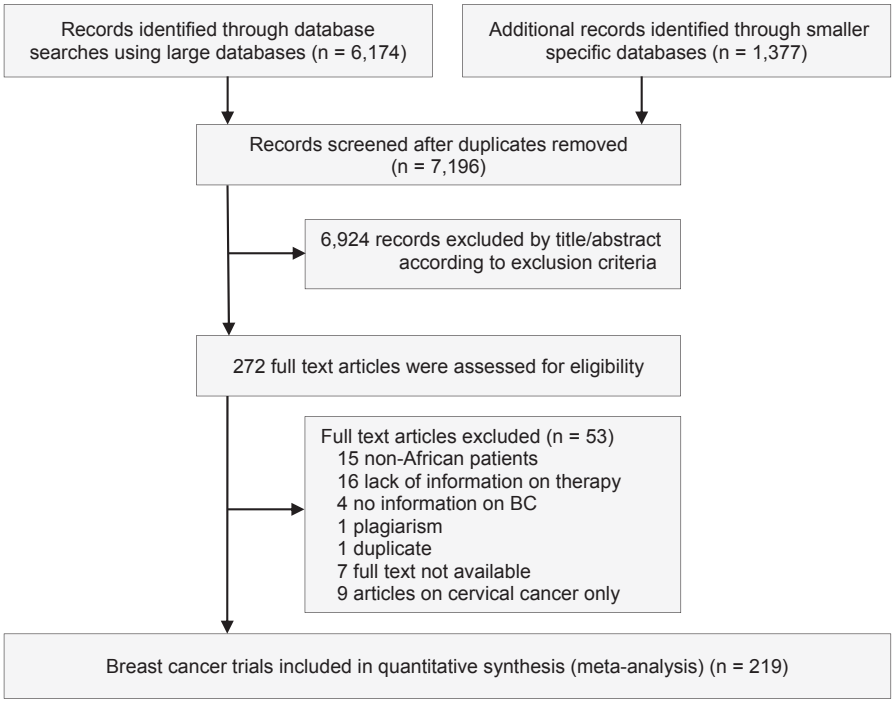

Fig. 1. Results of the systematic review: PRISMA flow chart.

rica) to group the results of our literature search. The scope of this systematic review is to give a quantitative overview on the articles available in the common large databases, as well as in the regional African databases, up until April 2014 on BC therapy and outcomes in Africa. For a qualitative review on BC care in general, we selected relevant articles less than 5 years old and added important previous work. First, we will give an overview on time trends, regional differences and the methodology of publications. Then, the relevant most recent articles on BC health care are discussed. Major challenges for BC care in Africa are summarized.

Methodology

We performed a systematic search in MEDLINE (Ovid), CENTRAL, African Journals Online (AJOL), African Index Medicus, The Breast Health Global Initiative, POPLINE, and SurvCan to identify all publications related to clinical and observational studies describing female cancer (breast and cervix) and Africa. Within this general search, we selected all publications related to treatment and/or outcomes in Africa. All publications were screened by title, keywords, abstract, and full text for relevant publications. Inclusion criteria were all studies describing treatment and/or outcomes of BC in Africa. Exclusion criteria were cross-sectional studies without information on therapy, studies on screening methodology, studies on pathologic material, studies only on African Americans, and studies conducted on non-African patients.

Additionally, we performed a search in MEDLINE (PubMed) for relevant topics on BC care, such as burden, awareness, risk factors, tumor biology, and healthcare services (PubMed search for 'Breast neoplasm AND Africa'). For this review, relevant articles from the last 5 years and selected articles from before are presented here as a brief overview, and major challenges are discussed.

Systematic Review on BC Treatment and Outcomes

This systematic review was carried out to review evidence on BC treatment in Africa.

Results and Discussion of the Search

Having used the above-mentioned inclusion and exclusion criteria to identify potentially relevant articles, we identified a total of 7,154 publications on the treatment of female cancer (BC and cervical cancer), of which we found 6,174 in the large databases:

Table 2. Publications according to years and top countries

	Total	2010–2014	2005–2009	2000–2004	1995–1999	< 1995
Nigeria	56	*16*[a]	*16*	8	1	15
South Africa	42	3	6	*9*	*8*	*16*
Egypt	33	15	10	3	3	2
Morocco	23	13	2	7		1
Tunisia	17	4	7	4		2

[a]Countries with the highest numbers indicated in italics.

MEDLINE (by Ovid; March 26, 2014; n = 5,745) and Cochrane (March 27, 2014; n = 429). We found 980 publications in smaller databases (AJOL; April 23, 2014; n = 281): African Index Medicus (May 7, 2014; n = 153), The Breast Health Global Initiative (May 7, 2014; n = 99), POPLINE (May 9, 2014; n = 340), and SurvCan (May 22, 2014; n = 107). In total, 938 publications were thought to be of relevance and the full papers were assessed. Of those, 219 publications were included in this review.

In general, we noted an increase in the number of publications available in the databases searched, from 15 articles in 1995–1999 to 72 articles in 2010–2014 (fig. 1). The majority of papers (n = 75) originated in North Africa (population in 2012: 207 million), closely followed by West Africa (n = 71; population in 2012: 320 million). Southern Africa (n = 42; population in 2012: 58 million) dominated before the year 2000. There were few publications from East (n = 19; population in 2012: 352 million) and Central Africa (n = 6; population in 2012: 133 million), but the number of studies has increased since the 1990s (table 1). This may reflect the socio-economic development of the countries and the availability of advanced medical service in the North African region.

When comparing the number of physicians per population, there are notable differences seen in the large countries of each region. Egypt and Algeria had the highest numbers (2.83 and 1.21 per 1,000 people in 2008 and 2007), South Africa had 0.77 per 1,000 people in 2004, Nigeria had 0.395 per 1,000 people in 2008, and Ethiopia and Tanzania had only 0.022 and 0.008 per 1,000 people in 2007 and 2006 [7]. This reflects the focus of primary healthcare mainly involving non-physicians in East Africa (e.g. Tanzania), as opposed to a more clinical approach with more physicians in West Africa. Since there are fewer physicians in East Africa, this can possibly explain the relatively low number of articles on BC therapy from this region.

Looking at the individual countries, we noted that Nigeria was the number one country in terms of the overall number of publications, and specifically since 2005. Before 2005, South Africa was the country with the most articles available. It is possible that the case of scientific misconduct during the high-dose chemotherapy BC trial from South Africa may have led to reduced activities in BC research [8]. Egypt, Morocco, Tunisia, and Ghana followed with an overall number of 10 or more articles (table 2). These data are in line with the large population size and advanced socio-economic status of these countries.

Types of Studies Published

The studies were classified based on the type of treatment, the study design, and the grading of levels of evidence (LoE) (supplemental table 1, *www.karger.com/?DOI=4433156).* The therapies described in the articles were mainly surgery (70%), followed by chemotherapy (60%), radiotherapy (46%), and endocrine treatment (38%). Targeted treatment was rarely described. We note that surgery was the main focus and probably also the most widely applied therapy for BC patients. Finding that 60% of articles analyze or mention chemotherapy may indicate that systemic therapy is also used. However, finding that only 38% of articles analyze endocrine therapy indicates an increased need for more focus on this inexpensive and well-tolerated treatment option [9].

In most cases, descriptive studies (43%) were conducted. We found few randomized controlled trials (9%) and only 25% trials in total. There were also 5% reviews. The influence of therapy was reported in 53% of the articles; median survival was reported in 28%. Toxicities were mentioned in 21%. We found 23 meta-analyses. When looking at LoE criteria according to the Oxford definition [10], most articles showed LoE 4 (72%).

Epidemiology of BC in Africa

Recently, a total number of the 26 population-based registries in 20 countries were assembled in the African Cancer Registry Network (AFCRN) and contributed data to the GLOBOCAN 2012 database [11]. The report estimated that the incidence rates vary nearly 4-fold across various regions of the world, with rates ranging from 27 per 100,000 in Middle Africa and Eastern Asia to 96 per 100,000 in Western Europe. Higher incidence rates occur in countries with established screening programs. BC is the most commonly diagnosed cancer in Africa annually, with an estimated 63,100 cancer deaths in 2012 [2, 12].

The incidence rates vary considerably within Africa. Population-based, age-standardized data from Kenya (Nairobi) revealed an age-standardized incidence rate of 52 per 100,000 in 2004–2008 [13]. Population-based data from Zimbabwe and Uganda during the same time period showed rates of 33 and 34 per 100,000 women, respectively [14, 15]. Results from Malawi (national data) are even lower, showing an annual incidence of 4 per 100,000 women [16]. Since registration methods are similar, reasons for this diversity may be lack of access to health service, lack of pathologic diagnosis, or true differences in risk factors.

Recently, several population-based cancer registries published their data analyzing trends over a period of 15–20 years. The 20-year incidence trend among the black population of Zimbabwe increased by about 4.9% annually, on average. The increases were more evident in older age groups (above age 50 years) than among the young [14]. In Uganda, the annual increase in incidence between 1991 and 2010 was 3.7% [15]. In Mozambique, the incidence of BC increased from 13.7/100,000 in 1991–1996 to 26.2/100,000 in 2003–2008, with relevant increases of 6.5% annually, on average. The greatest changes were seen among postmenopausal women

[17]. The possible reason for the increasing BC incidence was suggested as adoption of Western habits, especially among the urban population, leading to lower fertility rates and a higher frequency of obesity. In South Africa, a recent article from a rural area showed that the annual incidence in women was only 12.2 per 100,000 in 2012, with an annual increase of 4.3% since 1998. It is likely that reproductive factors and the lifestyle in the rural areas are still protective against BC, but even here changes are being noticed [18].

Altogether, increases in age-standardized BC incidences of between 3.7 and 6.5% annually are seen. This alarming fact has to be considered when planning healthcare service capacities and awareness campaigns for the upcoming years.

Risk Factors and Prognostic Factors of BC in Africa

A different picture of BC in Africa concerning the incidence, the tumor biology, and the population and its risk factors and outcome is seen. Comparing Caucasian and African American patients has revealed differences in tumor biology leading to differences in outcomes. Lower incidence rates, but higher mortality, are reported. Younger age and a higher risk of triple-negative tumors lead to reduced survival in African Americans [19]. The majority of African studies are hospital-based case-control studies with small numbers.

Brinton et al. [20] reviewed the literature on risk factors for BC in African women. Higher parity (as in Africa) is generally considered protective – but may possibly lead to a transient increase in risk for premenopausal BC, with subsequent decreases at the postmenopausal age. Breastfeeding as a protective factor was found, but some studies only showed a weak or no effect. Higher socioeconomic status was found to be a risk factor in several studies; this could also be a surrogate for the prevalence of other risk factors (obesity, fewer children, etc.). In addition, better health-seeking behaviors may increase the number of diagnoses made in the higher socio-economic bracket. A strong correlation between BC and height was found in several studies, as well as the correlation between higher waist circumference and waist-to-hip ratio to BC risk. A large case-control study from South Africa revealed increases in BC risk during the use of hormonal contraceptives, especially progesterone-alone (injectable) options [21]. There is, up to now, a lack of epidemiological studies addressing environmental factors, physical activity, medical history, toxic agents, and most dietary factors including alcohol. Factors unique to Africa may include infectious agents such as the microbiome, human immunodeficiency virus (HIV) prevalence, and malaria. Environmental agents, such as fertilizers, insecticides including DDT, skin lighteners and hair relaxers, may also influence the susceptibility to BC [20].

BC incidence rates are very low in North Africa. Corbex et al. [22] postulated that the risk factors are similar throughout Africa but that the prevalence varies considerably. They looked at the pattern of risk factors in North Africa compared to Western countries to see if this may explain the low rate of BC, as well as the unique patterns of BC in North Africa, such as early onset, aggressive forms (e.g. inflammatory BC), or high proportions of male BC. In North Africa, the presence of protective factors, especially during the 1980s, was more dominant than in Western countries. The mean number of children, early age at first childbirth, longer duration of breastfeeding, higher age at menarche, early menopause, little use of hormonal contraceptives, less alcohol consumption, and lower body mass index lead to a low-risk profile, which is now more evident in the elderly than in the younger North African women.

When looking at age-specific incidence rates, young age groups show similar BC rates compared to Western countries whereas the older age groups (above age 50 years) have markedly reduced incidence rates. Lack of screening in older age groups may also lead to lower detected incidence rates. Thus, the proportion of BC at a young age is higher due to a lower detected incidence in older women, and does not necessarily reflect different African tumor biology. The same applies to male BC, where the proportion is higher due to lower numbers of postmenopausal BC in women. The lower incidence of BC in postmenopausal women also leads to higher proportions of inflammatory BC, as reported in various case series. These observations may explain the difference in the BC pattern in North Africa, which does not necessarily point to a different biology of the disease but rather to a difference in the population structure [22].

Eng et al. [23] published a large meta-analysis on articles describing hormone receptor status and human epidermal growth factor receptor 2 (HER2) status in Africa. They reported on 80 studies, including nearly 17,000 tumors. The proportion of estrogen receptor-positive disease was between 20 and 80%. Influencing factors on the proportion of estrogen receptor-positive disease included the use of archived tissue compared to prospectively collected tissue, the year of collection, and the higher proportion of grade 3 tumors, which had less estrogen receptor-positive cases. The more recent and prospectively collected series showed that the majority of cases were estrogen receptor positive. This should encourage the use of tamoxifen as a simple and inexpensive treatment option, even in cases where the receptor status is unknown.

In summary, reproductive and lifestyle risk factors according to small studies from Africa were found similar to those in Western patients, but differences in population structure and risk factor prevalence have to be considered when looking at patient cohorts from Africa. It is possible that larger cohort studies would reveal differences in known risk factors and there could also be unique factors (e.g. fertilizers, co-infections) that contribute to the BC risk in Africa.

Clinical and Pathological Presentation of BC

Clinical and pathological factors will be discussed on the basis of articles from 7 African countries: Republic of South Africa (RSA) [24], Egypt [25–27], Nigeria [28], Eritrea [29], Morocco [30], Cameroon [31, 32], and Rwanda [33].

All articles reported that the majority of women presented at the healthcare facility with advanced BC (stages III and IV). Factors that influence the lack of early healthcare-seeking practices include distance to the healthcare facility (RSA and Egypt), the tendency to wait until experiencing pain (Egypt), a lack of knowledge regarding breast self-examination (Egypt), residing in a rural area (RSA), advanced age (RSA and Egypt), low literacy rates (RSA, Egypt, Nigeria), low income (RSA and Egypt), lack of knowledge regarding the illness (Nigeria), pursuing traditional treatment and the belief in supernatural healing. Being single and premenopausal were also risk factors for delayed presentation and diagnosis (Nigeria).

The majority of the patients described were ≤ 50 years old (all articles). 3 papers reported on male BC, with a proportion between 1 and 6% (Cameroon, Rwanda, and Eritrea). Self-examination was found to be the primary method of first detecting the BC, but very few patients underwent other examination procedures (Cameroon). At the time of the initial diagnosis, the majority of the women had already developed clinically positive lymph nodes and had major organ metastasis, mainly to the lungs, bones, and liver (Cameroon, Eritrea).

In conclusion, there is a low level of early health-seeking practices among women with BC in Africa. Sociodemographic, economic, and behavioral factors lead to advanced cancer stages by the time the women present for diagnosis. Specifically identifying the problematic areas and approaching them will contribute to improving BC patient outcomes by reducing the average stage at presentation ('downstaging').

Surgery and Adjuvant Treatment of BC

Considering the limited facilities for radiation, mastectomy is the surgical treatment of choice for operable cases in many African countries. In Nigeria, 35.2% of the newly diagnosed BC patients (n = 1,226) underwent mastectomy, and half of these had received primary systemic chemotherapy. The majority of patients were treated with palliative intention without surgery due to advanced disease [34]. A case series from Egypt analyzing breast tumor management found that over half of the patients presented with stage III or IV BC. Of all surgical cancer cases, 68% were treated by modified radical mastectomy; the authors suspect that surgeons prefer this option since compliance to radiotherapy after breast conservation may be poor despite available facilities [35]. The lack of availability of radiotherapy still remains a significant challenge, with an estimated current coverage of 28% and the need for another 703 machines in Africa [36].

Primary systemic chemotherapy is an important treatment component when looking at the high proportions of advanced disease. A phase II trial from Nigeria that included 16 patients who received primary systemic capecitabine for over 24 weeks found that the overall response was 44% after 8 cycles [37]. A study from Egypt reported on gemcitabine and cisplatin in locally advanced or metastatic BC after previous anthracycline therapy. In 132 patients, there was a 33% response rate and a 46% rate of stable disease was seen [38]. A study from Egypt compared anthracycline-based chemotherapy with or without docetaxel in estrogen receptor-positive pT1–2 BC (n = 60). The addition of taxanes did not improve the 4-year disease-free survival [39].

Altogether, we found only a few articles of clinical trials conducted in Africa and especially addressing specific features such as advanced stage, treatment availability, and comorbidities (e.g. HIV infection).

Cancer Control in Africa

We reviewed articles in the African context related to the health system efforts made for prevention, screening, and treatment to reduce the burden associated with BC. There are studies that suggest early detection and intervention as cost-effective ways to avert the daily-adjusted life years lost (DALYS). One study discussed that mammography screening, in combination with treatment at all stages, is a cost-effective intervention for BC that would likely prevent more DALYS [40]. However, others argue that biennial screening by clinical breast examination (CBE) and rising mass media awareness were more effective at reducing the DALYS than mammography screening [41]. Mammography screening may become the preferred option in the future, but currently, due to the very young population which is not eligible and due to resource constraints, this option is not suitable for the majority of Africa's sub-Saharan countries [42].

In Ethiopia, it was found that the women's first visits to the healthcare service providers were initiated due to changes in or the addition of symptoms, family pressure, or secondary to other care-seeking behaviors [43]. The patient navigation chain has a lot of barriers until the patients eventually reach the central cancer center. At a minimum, patients face 3 or more nodes that are widely divergent [44]. A study done in Ghana found that being a member of the Islamic religion, seeking treatment at traditional healers, and a lack of awareness of national health insurance coverage for BC treatment were the main factors that affected treatment completion [45]. A hospital-based study from Ghana revealed that patients diagnosed with late-stage cancer who were put on adjuvant therapy with hormone receptor status evaluation were more adherent to the treatment guidelines compared with those that never had the hormone receptor status determined [46]. A population-based survey from Rwanda and Sierra Leone, looking at the prevalence of breast masses and barriers to care, showed that women were not seeking medical care due to the absence of symptoms of the breast masses, financial issues, and trust in traditional healers, as well as an overall distrust towards the medical system [47].

Late stage at diagnosis is a problem for BC control [40, 48, 49]. In Ghana, a study showed that 64.1% of patients presented to facilities at a late stage of the disease for diagnosis [46]. There are significant efforts being made to optimize treatment with limited resources; for example, Rwanda established a central BC treatment center [50]. Authors from Tanzania demonstrated that a cost-ef-

fective low-technology interventional study resulted in an improvement of early detection and downstaging at diagnosis. Proactive visitation of health aides to the villages for the early detection of BC and other cancers was effective. The study found an increasing number of early-stage BCs (stages I and II) in the intervention villages during the 1st, 2nd, and 3rd year at 9%, 60%, and 67%, respectively [49].

In summary, early detection and treatment are the main interventional approaches for BC control. The patient's sociodemographic and behavioral factors, community culture and beliefs, healthcare service availability, and navigation-related factors are important considerations for BC control programs. Interventions to improve the outcomes and the overall healthcare system, like a combination of treatments at all stages, awareness generation by media coverage, the use of community health workers, and the use of health data based on research, are very effective. Resource constraints are very demanding in making use of and sustaining such interventions. Resource-stratified guidelines for BC were recently published as an initiative from the National Comprehensive Cancer Network [51]. The 4 levels are 'Basic', 'Limited', 'Enhanced', and 'NCCN Guidelines at centers of excellence in the United States'. These guidelines can be adapted according to the individual setting.

Conclusions

BC is an emerging topic in Africa according to the annually increasing numbers of published articles. Still, evidence on therapy and outcome is mainly available from cohort studies. Up to now, only few prospective clinical trials have been published that include issues specific to Africa, such as patients with young age and advanced tumor stages, co-infections, and limited resources. By now, data from population-based cancer registries have become available for the majority of African countries. Age-standardized BC incidence rates show regional differences and increase over time. The reasons include better diagnosis and changing risk factors in a population in transition, like, e.g., reproductive factors, lifestyle, etc. African physicians are faced with many young patients due to the shape of the African population pyramid and with late-stage tumors due to delays in accessing health care. Mastectomy is the surgery of choice because of a lack of radiation facilities; primary systemic therapy as an option for locally advanced disease is available in oncology centers. As compared to earlier reports, recent studies show higher proportions of estrogen receptor-positive cases, suggesting advantages of endocrine therapy for patients with unknown receptor status. Cancer control in Africa mainly involves activities to downstage the cases at presentation and to equip the healthcare systems with capacities to provide regional and systemic treatment. This needs political prioritization and efforts of the scientific community to provide evidence for the specific African context.

Online Supplemental Table

Supplemental Table 1. Publications on breast cancer according to topic, design, and region, with the population in 2012 indicated

To access the online supplemental table, please refer to *www.karger.com/?DOI=4433156.*

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EPIDEMIOLOGY

Survival of breast cancer patients in rural Ethiopia

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Abstract

Purpose To describe the histopathological characteristics and survival of female breast cancer (BC) patients in a rural setting with limited access to adjuvant treatment.

Methods A prospective study of 107 histologically confirmed BC patients treated with surgery from 2010 to 2016 from rural parts of western Ethiopia. Referral pathology was performed, and active follow-up was conducted. Adjusted cox regression analysis (hazard ratio [HR]) was performed.

Results The median age at diagnosis was 45 (16–83) years; 57% of the patients presented with cT3/4 tumors, 71% with clinically positive lymph nodes, 21% with HER2-overexpression (Dako3+) and 68% with grade 3 tumors. Estrogen and/or progesterone receptor expressions were present in 66% and triple-negative disease in 25%. The estimated 1- and 2-year overall survival probability rates were 78 and 53%, respectively. The 2-year survival for patients with clinically positive lymph nodes was 44% compared to 73% for patients with lymph node-negative disease (HR 2.44; 95% confidence interval [95% CI] 1.19–5.02). The corresponding 2-year survival for patients with cT4 tumors was 25% versus 68% for patients with cT1–2 tumors (cT1–3 vs. cT4 HR 3.86; 95% CI 1.82–13.63). The 2-year survival for patients with hormone receptor-negative disease was 40% compared to 59% for patients with hormone receptor-positive disease (HR 1.92; 95% CI 1.06–3.47).

Conclusion The majority of breast cancer patients treated with surgery in rural parts of western Ethiopia are diagnosed at advanced stage and have hormone receptor-positive disease. Nearly half of the patients die within 2 years. These findings underscore the need for provision of adjuvant hormonal therapy and for the establishment of pathology service including hormone receptor testing.

Keywords Breast cancer · Africa · Survival · Prognostic factors · Ethiopia

Abbreviations

BC	Breast cancer
HR	Hazard ratio
TN	Triple negative
ER	Estrogen receptor
PgR	Progesterone receptor
IHC	Immunohistchemistry
ENCR	European network of cancer registries
MFS	Metastasis-free survival
NST	No special type
FISH	Fluorescence in situ hybridization
CI	Confidence interval

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Introduction

Breast cancer (BC) is known to be the most common malignant disease in women worldwide and also in Ethiopian women [1]. BC incidence gains importance in Sub-Saharan Africa, attributed to a westernized lifestyle, a growing and aging population [2]. This brings a double burden of communicable and noncommunicable diseases to these regions. Despite the growing burden of cancer cases of all sites, there are limited data available on characteristics, treatment, and survival of BC patients in Sub-Saharan Africa, and these data are mostly collected in urban BC cohorts [3]. According to Globocan 2012, the age-standardized incidence rate and mortality of BC in Ethiopia are estimated to be 41.8/100,000 and 23/100,000, respectively [1]. In 2015, Ethiopia had about 99.39 million inhabitants [4] of which only 16% were urban population. About half of the population (47%) was under the age of 15; in rural areas, two in three women could not read or write [5, 6]. In Ethiopia, 70% of deaths are caused by communicable disease and injuries, neonatal, infant, and maternal mortality [7]. A National Cancer Control plan has first been implemented in 2015 [8]. In 2015, life expectancy rate at birth for male and female were 63 and 67, respectively. The total expenditure on health per capita was 73 Dollar in 2014 [4].

Similar to data from surrounding countries, women with BC in Ethiopia usually present with locally advanced disease. Among 655 BC patients in Addis Ababa, 71% had stage 3 disease [9], and in Uganda and Kenya, 80 and 62% of the patients had stage 3 disease [10, 11]. Compared to the western world, Ethiopian women present at a young age. Kantelhardt et al. found a median age of 43 years [9]. This finding is similar to data from neighboring Kenya and Uganda where patients had a similar median age [10, 11]. In Addis Ababa, among 325 patients, 65% showed hormone receptor expression [12], and in Kenya, 73% of BC patients were diagnosed with estrogen receptor (ER) positive [11]. The findings of BC being mainly hormone receptor positive are supported by a systematic review and meta-analysis of Eng et al. [13]. A lack of awareness and knowledge about painless breast lumps has been described in African literature as well as long intervals from onset of the first symptoms to the presentation at a medical doctor [14]. Among 1070 BC patients in Addis Ababa, a metastasis-free 5-year-survival rates of 72% (stages 1 and 2) and 33% (stage 3) were found [9]. In Kampala, Uganda, a 5-year-survival of 56% (74% early stage, 39% advanced stage) was reported [15]. In Ethiopia, radiation and chemotherapy are available to the public at the radiotherapy center of the Addis Ababa University Hospital. Surgery is performed by general surgeons at primary care level and accessible in many hospitals throughout the country as well as in our study site in Aira.

Aira hospital is a rural primary care hospital located about 500 km from the capital Addis Ababa in the remote rural area of Oromyia in western Ethiopia. It provides health service for roughly 500,000 people. About 90 surgical procedures of the breast are performed per year. Clinical staging is standard, patients with symptoms received chest X-ray and/or abdominal ultrasound; bone scintigraphy is not available. BC patients are treated by surgery only. Modified radical mastectomies with axillary dissection of levels 1 and 2 are performed in case of clinically manifest BC. In cases of inconclusive clinical finding or patient's refusal of mastectomy, quadrantectomy and lumpectomy only were performed. There is no local diagnostic facility for pathological evaluation of surgical tissues, with the nearest pathology service located at 500 km farther away in Addis Ababa. Similarly, adjuvant chemotherapy and radiation were not available in Aira. For patients enrolled in this research project, however, patients with hormone receptor-positive disease were offered Tamoxifen therapy (distribution starting from 2013).

In this study, we describe the tumor characteristics, survival, and prognostic factors of breast cancer patients treated with surgery in rural parts of Ethiopia, being the first of its kind in Sub-Saharan Africa.

Methods

A prospective observational study of 107 breast cancer patients, treated with surgery in rural western Ethiopia (Aira Hospital) from January 25, 2010 to July 28, 2016 and actively followed for survival, was performed. Breast tissue was immediately stored in 4.5% buffered formalin. The samples were evaluated by referral pathology in Halle, Germany. Standard hematoxylin and eosin staining and immunohistochemistry (IHC) were performed. Grading was determined according to Elston and Ellis [16]. ER and Progesterone Receptor (PgR) testing (Dako, Carpinteria, California) was considered positive in specimen with $\geq$ 1% positive cells [17]. In HER2 testing (HercepTest, Dako, Carpinteria, California) Dako score 3 + was declared positive, while Dako scores 2 + , 1 +, and 0 as negative. Ki-67 was grouped in $<$ 10%, 10–30% and $>$ 30% [18]. Clinical tumor size (cT) and clinical involvement lymph nodes (cN) were provided by the local surgeon; pathological T and N were not ascertained due to logistic reasons, and thus, the potential differential diagnoses of clinically positive axillary lymph nodes could not be ascertained. Symptoms or proof of metastases at first diagnose were documented by the surgeon. For cT-, cN-, and cM-Staging the "Condensed TNM for Coding the Extent of Disease—ENCR Recommendations" was applied [19]. Surgical margins were evaluated clinically. Tumor types according to immunohistochemistry defined as proposed

by Minckwitz et al. were as follows: Luminal A-like tumors (ER positive and/or PgR positive; HER2 negative, grade 1 or 2), Luminal B/HER2-negative-like tumors (ER positive and/or PgR positive; HER2 negative, grade 3), Luminal B/HER2-positive-like tumors (ERpositive and/or PgR positive; HER2 positive, all grades), HER2-positive-like (nonluminal) tumors (ER negative and PgR negative; HER2 positive, all grades), triple-negative (TN) tumors (ER negative, PgR negative, HER2 negative, all grades) [20].

Two times (February 2013 and 2016), female patients with histologically confirmed newly diagnosed invasive carcinoma of the breast (ICD codes C50.0-9) or their families were visited in their houses. When distance was too far, telephone contact was arranged ($n = 4$). An experienced local nurse conducted interviews with the patients or in case of death, with the closest family members. A standardized questionnaire translated to the local language "Afaan Oromo" was used. Pseudonymized descriptive patient data were analyzed using SPSS, Version 22 (IBM, Armonk, United States of America). The median follow-up time was calculated using the reverse Kaplan–Meier method [21]; it included follow-up time of all censored and deceased patients. The primary endpoint of the study was death of the patient, regardless of its cause. The day of the first institutional consultation for the suspected cancer was defined as date of diagnosis according to international coding standards for cancer registries [22]. Survival time was defined as time from date of diagnose to date of last contact or death. Death certificates were not available. Overall survival analysis was performed using Kaplan–Meier estimator method, and Log-Rang-test to determine p value was carried out selectively. Prognostic factors were determined by multivariable Cox's proportional hazards model, and established independent prognostic factors were included into the model. Hazard ratios (HR) were presented with 95% confidence intervals (CI).

Ethical approval was obtained by Addis Ababa University Medical Faculty and Martin-Luther University, Halle. Individual consent was obtained from all patients included in the study.

Results

The median follow-up time of all 107 patients was 28 (range 0–71) months. The median age at diagnosis was 45 years ($n = 107$, ranging from 16 to 83 years), the majority of women were found in the age group of 35–50 years (Table 1).

The median travel time to the hospital was 5 h; 41% of the patients needed more than 7 h to reach the hospital [information available (i.a.) $n = 86$]. The median number of births per woman was 5 (i.a. $n = 87$, range 0–12), and women were breastfeeding for a median duration of 8.5 years (i.a. $n = 74$). Of the 78 women with information on education available, 73% were illiterate. Almost half of the patients consulted the hospital after more than 12 months from onset of symptoms (i.a. $n = 92$). Of all patients, five reported known BC of family members, and in all cases sisters were mentioned. In addition, one patient's daughter was affected. Genetic testing

Table 1 Clinical and pathological characteristics of the cohort

Characteristic (n = number of cases with information available)	Number	Proportion (%)
Total number	107	100
Age (median 45, range 16–83 years)		
< 35	26	24.3
35–50	54	50.5
> 50	27	25.2
Years of diagnose ($n = 107$)		
2010–2012	62	57.9
2013–2016	45	42.1
Time to presentation* ($n = 92$)		
0–6 months	24	26.0
7–23 months	34	37.0
> 23 months	34	37.0
Travel time to hospital (n = 86)		
< 3 h	15	17.4
3–6 h	36	41.9
7 h or more	35	40.7
Type of surgery ($n = 90$)		
Mastectomy	69	76.7
Lumpectomy/quadrantectomy	21	23.3
Tumor size ($n = 103$)		
cT1 (≤ 2 cm)	4	3.9
cT2 (> 2–5 cm)	40	38.8
cT3 (> 5 cm)	42	40.8
cT4	17	16.5
Lymph nodes ($n = 103$)		
cN positive	73	70.9
cN negative	30	29.1
Distant metastases		
cM positive	7	6.5
Stage (according to ENCR**) ($n = 102$)		
Localized	27	26.5
Local spread	2	1.9
Regional spread	66	64.7
Advanced	7	6.9
Tamoxifen (in receptor-negative disease $n = 69$)		
Yes	29	42.0
No	40	58.0

*Self-reported time to presentation at the hospital from first onset of symptom

***ENCR* condensed TNM for coding the extent of disease—ENCR recommendations

was not available. The majority (77%) received mastectomy as surgical therapy, and about three in four patients treated by mastectomy simultaneously received axillary lymph node dissection. Only two of the patients received (neo)adjuvant chemotherapy or radiotherapy. During the time of follow-up, 42% (29/69 patients) of the patients with hormone receptor-negative disease ever received Tamoxifen. many patients (38.1%) did not adhere to the recommended follow-up visit at the hospitals, with 27.4% of the patients visiting the hospital only once, while 34.6% of the patients visited more than once.

Patients predominantly presented with large tumors. Of 17 tumors classified cT4, only four were inflammatory BCs. In 71% of the cases, positive lymph nodes were found by palpation. Clinical signs of distant metastases were documented in only seven cases; however, it was not routinely confirmed by imaging techniques (see Table 1).

The predominant histologic type was ductal carcinoma of no special type (NST). A large proportion of breast cancers (68.2%) were poorly differentiated. In line with this finding, 45.2% showed a high Ki-67 expression (> 30%), HER2 was found to be overexpressed (Dako3+) in 23 cases (21.9%). Two-thirds of the tumors showed hormone receptor expression; ER+ PgR+ tumors were predominant with 30.5% (see also Table 2). In 27 cases (24.8%), triple-negative BC was found.

During the follow-up visit at the patient's house, death of 57 patients (53.3%) was confirmed by relatives. The estimated 2-year overall survival probability of all patients was 53% (see Fig. 1). The estimated 2-year survival probability for patients with clinically positive lymph nodes was 44%, and for patients with negative lymph nodes, it was 73% (see Fig. 2). The corresponding survival probability of patients with a tumor size ≤ 5 cm (cT1/2) was 68%—with a tumor size > 5 cm (cT3) 45%, with tumors classified by cT4 25% (see Fig. 3), with hormone receptor expression 59%, and without hormone receptor expression 40% (see Fig. 4). The estimated 1- and 2-year survival probability rates of patients with triple-negative BC were 58 and 42% and with no triple-negative disease being 85 and 57% (Table 3).

To determine the influence of prognostic factors, multivariate analysis with Cox's proportional hazards model was carried out including age, tumor size (cT), lymph node involvement (cN) and hormone receptor expression. There was a tendency for very young women (< 35 years) to have a worse overall survival compared to patients ≥ 35 years with a hazard ratio of 1.67 (0.88–3.15). Patients with cT4 tumors seem to have a worse overall survival than patients with tumors staged cT1–3 (HR 3.86, 1.82–13.63). Patients with clinically positive lymph nodes had a worse overall survival than patients with negative lymph nodes with a HR of 2.44 (1.19–5.02). Patients with hormone receptor-negative disease showed a worse overall survival than patients with hormone receptor-negative disease with a HR of 1.92 (1.06–3.47).

Table 2 Histologic and immunohistochemical characteristics of the cohort

Characteristic (n = number of cases with information available)	Number	Proportion (%)
Total number	107	100
Type (n = 106)		
NST (ductal carcinoma of no special type)	97	91.5
Lobular	1	0.9
Other	8	7.6
Grading (n = 107)		
1	6	5.6
2	28	26.2
3	73	68.2
Hormone receptor (n = 105)		
Positive	69	65.7
negative	36	34.3
ER (n = 105)		
Positive	47	44.8
Negative	58	55.2
PgR (n = 105)		
Positive	54	51.4
Negative	51	48.6
Receptor expression (n = 105)		
ER+ PgR+	32	30.5
ER+ PgR−	15	14.3
ER− PgR+	22	20.9
ER− PgR−	36	34.3
Ki-67 (n = 104)		
< 10%	19	18.3
10–30%	38	36.5
> 30%	47	45.2
HER2 (n = 105)		
Positive (Dako 3+)	23	21.9
Negative	82	78.1
Type according to IHC* (n = 105)		
Luminal A-like	22	20.9
Luminal B-like HER2−	34	32.4
Luminal B-like HER2+	13	12.4
Her2-positive, ER− PgR−	10	9.5
Triple-negative	26	24.8

**IHC* immunohistochemistry, groups according to Minckwitz [20]

Discussion

In this study, we describe the tumor characteristics and survival of 107 consequently enrolled BC patients treated with surgery in rural Ethiopia. About three-quarter of patients

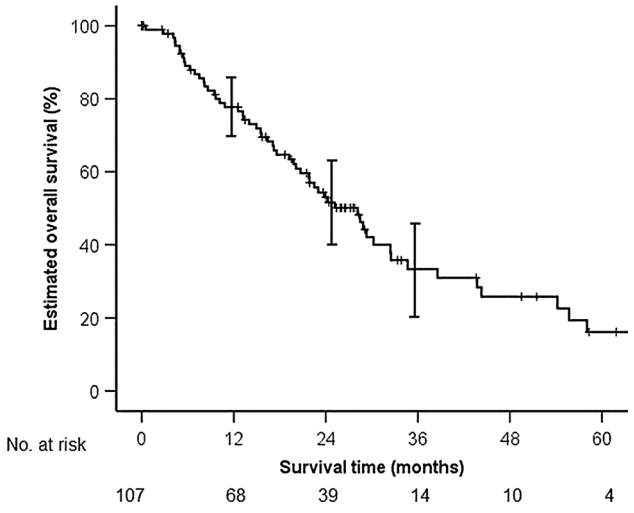

Fig. 1 Kaplan–Meier plot of estimated overall survival of total study population

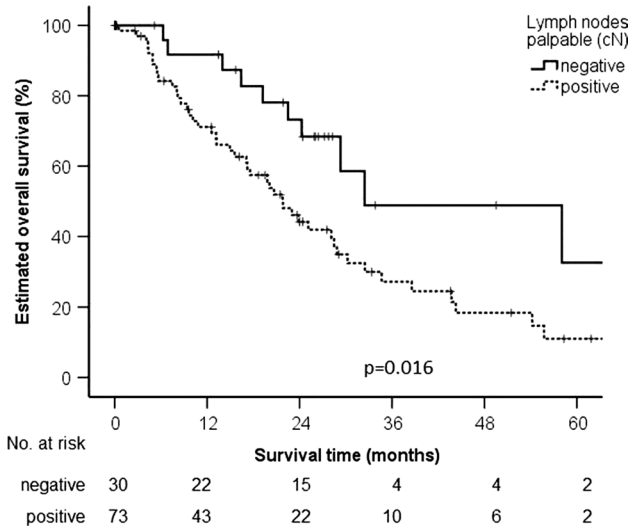

Fig. 2 Kaplan–Meier plot of estimated overall survival according to clinical lymph node involvement

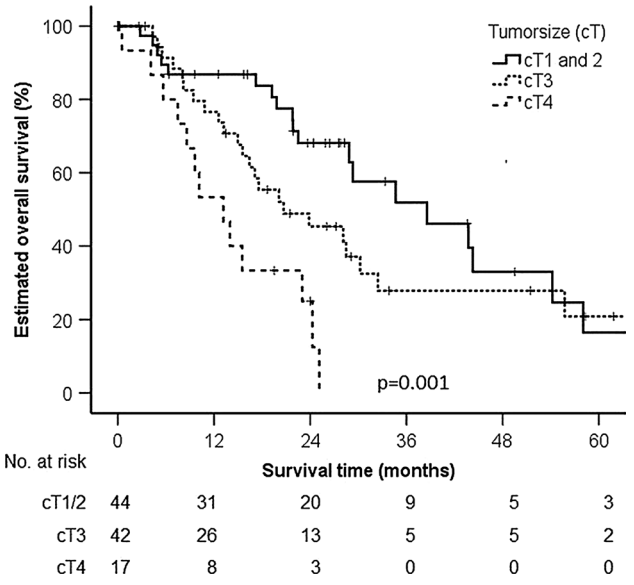

Fig. 3 Kaplan–Meier plot of estimated overall survival according to tumor size (cT)

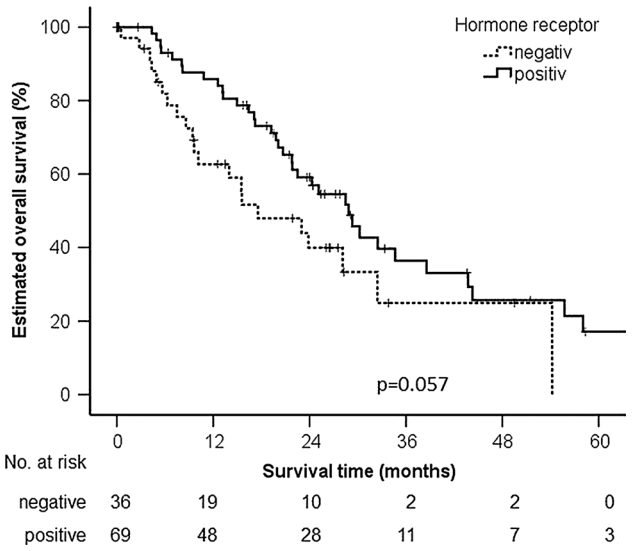

Fig. 4 Kaplan–Meier plot of estimated overall survival according to hormone receptor expression

were < 50 years old, with the majority presenting with advanced disease. Most tumors were hormone receptor-negative disease. Overall 2-year-survival probability of these operated patients mostly without adjuvant therapy was 53% (95% CI 42–64%), with the survival much lower for patients diagnosed with cT4 tumors, hormone receptor-negative disease and clinically positive lymph nodes.

In accordance with the young Ethiopian population structure, the median age was 45 years; patients were younger than in western study populations (median age at diagnose in the US 62 years) [23]. These findings are in line with other hospital cohorts. In Addis Ababa the median age of 1070 BC patients was 43 years [9], in Kenya the median age among 304 BC patients was 47.5 years [11], in Uganda 45 years [10]. The young age can probably mostly be attributed to the young age structure of Ethiopian society. In rural Ethiopia, 49% of the population is under the age of 15 and only 9% > 50 years old [5]. Data from the only Ethiopian population-based cancer registry show an age-standardized incidence rate of 40.6 per 100,000 population for Addis Ababa city. Incidence rates in the younger age groups were reported similar to Western countries with lower rates in the older age groups [24]. Due to the large proportion of young women

Table 3 Prognostic factors according to Cox's proportional hazards model

Factor	Hazard ratio	95% confidence intervals	*p*-Value multivariate
Age			
< 35 vs. ≥ 35 years	1.67	0.88–3.15	0.114
Tumor size (cT)			
cT1–2 vs. cT3	1.30	0.69–2.46	0.420
cT1–3 vs. cT4	3.18	1.44–7.04	0.004*
Lymph nodes (cN)			
Negative vs. positive	2.44	1.19–5.02	0.016*
Hormone receptor			
Negative vs. positive	1.92	1.06–3.47	0.032*

*Statistically significant

in the country, total numbers of young patients were high. Consistent with reports of other east African study populations, patients in our cohort sought medical advice with a significant delay, and 46% waited more than 12 months since onset of the symptoms. Dye et al. found a mean time to presentation of 1.6 years in 69 BC patients in Addis Ababa and displayed the problem that the painless lump did not trigger action in most patients, but additional symptoms like pain or itching [14]. These findings highlight the need for education on early symptoms of BC.

Most patients in our study population were affected by an unfavorable tumor stage with a large tumor size (cT3 and cT4: 57.3%) and clinically positive lymph nodes (cN positive in 70.9%). The clinical examination may be an overestimation since other possible diagnoses of clinical lymph node enlargement could not be histologically verified (pN not available). On the other side, there might be an underestimation since small lymph node metastases could have clinically been missed. Nevertheless, the proportion found cN positive matches data from Addis Ababa, where 81% of 882 BC patient had histologically confirmed lymph node metastases. Similar to our patients, mean tumor size in the Addis Ababa cohort was large (4.96 cm) [9]. The presentation at late stages is a problem across Sub-Sahara Africa as reported by Jedy-Agba et al. (review) with proportions of stage 3 and 4 disease from 30 to 100% [25].

In our study population, 65.7% of the tumors showed hormone receptor expression; 44.8% were ER and 51.4% PgR positive. This finding is in line with study results from a hospital cohort in Ethiopian capital city Addis Ababa, the authors similarly 65.3% ER-negative tumors [12]. Studies from surrounding eastern African countries found 73% ER-negative disease in Kenya [11], 47% in Uganda [10] and 48% in Tanzania [26]. Based on a systematic literature review of hormone receptor status results from Africa, Eng et al. found that the tumor biology in Africa is very diverse—but recent studies from Africa report similar proportions of ER-negative BC compared to the West [13]. The problem of inadequate tissue handling, fixation, and embedding leading to false-negative hormone receptors has been discussed in the literature. In our case series also, prolonged fixation times due to logistic challenges could also have led to false-negative ER status. This could explain the relatively high proportion of 21.0% ER− PgR+ tumors which are usually considered rare or artifact [27]. In conclusion, when considering ER and PgR as predictive factor, we found 65.7% of tumors to be hormone receptor positive and thus eligible for endocrine therapy.

Reports of the prevalence of triple-negative BC are equally heterogeneous [28, 29]. In our cohort of patients, 24.8% had triple-negative disease. Tanzanian reports mention 28% of triple-negative cases [25] whereas McCormack in South Africa found 21% triple-negative BC in her study [30]. Grading in our cohort was also unfavorable. We found 68.2% of poorly differentiated tumors, whereas among patients in Addis Ababa, only 25% had grade 3 tumors. The prevalence of poorly differentiated tumors shows a large variety between 25 and 67% among studies from eastern Africa [9–11, 31].

There are few reports about survival of women with BC in Sub-Saharan Africa. We compared overall survival in our surgery-only cohort (only two patients with chemotherapy) from rural Aira with the results of metastasis-free survival from urban stage 1–3 Addis Ababa patients ($n = 1007$, information on metastasis-free survival but not overall survival available), and we found the following differences: The rural Aira patients showed an estimated 2-year overall survival probability of 53%. Among Addis Ababa patients, metastasis-free survival (MFS) after 2 years was far more favorable (74%). In the Addis Ababa analysis, women with stage 3 disease showed a less favorable prognosis with a hazard ratio of 2.62 compared to stage 1 and 2. In the same study, very young patients (< 30 years old) had an unfavorable 5-year MFS of 13% and a hazard ratio of 3.2 compared to patients aged 50–59 [9]. This is in contrast to our results where patients < 35 years had a hazard ratio of 1.67 compared to patients ≥ 35 years. In our study cohort, only two patients received chemotherapy elsewhere. The remarkable contrast of low survival rate in rural Aira compared to Addis Ababa might reflect the lack of access to adjuvant treatment of women living in rural areas. Poor patients weakened by advanced disease living in rural areas are not very likely to seek medical treatment in the capital. Another reason for worse outcome in the rural Aira cohort is probably inclusion of patients with initial distant metastasis in the cohort due to lack of diagnostic facilities for staging.

Among 297 patients from an Ugandan cohort who mostly received adjuvant therapy an overall 5-year survival of 56% is reported. Patients with stage III and IV disease showed a

less favorable survival with an overall 2-year survival rate of 56% compared to 94% in patients with stage I and II. This survival rates are similar to our overall 2-year survival rate of 46% [10]. Data from another Ugandan study include 162 patients from the Kampala cancer registry and report a 1- and 3-year absolute survival of 72.0 and 54.3%, respectively [32]. Among 128 black BC patients from Harare, Zimbabwe, a 1- and 3-year absolute survival of 71.5 und 50.6% is reported [33]. It is notable that all data used for comparison come from urban cohorts and cancer registries with access to adjuvant treatment options. In our literature reviewing process, no survival data from rural hospital cohorts was found.

In our cohort, the estimated median survival time was 28 months. A noteworthy historical report deals with the survival of patients with untreated BC. In the years 1805–1933, 250 British patients with mostly stage 3 and 4 disease showed a median survival of 32 months [34]. A review of 1022 cases from the 19th and beginning of 20th century revealed a median survival of 29 month [35]. Thus, the overall survival in our cohort with mostly surgery alone is similar to historical cohorts of untreated BC patients. In our cohort surgery alone probably did not have a strong effect on survival, still in the rural setting it was important to achieve local cancer control and improve quality of life of the patient.

Strength of this investigation is the prospective design and the active follow-up (home visits) which gave us reliable survival status. The tumor specimens were evaluated with standardized protocols by one central referral pathology. However, our findings based on hospital case series may not be representative of all patients as it may exclude patients who did not seek medical consultancy for many reasons such as financial restraints, too ill to travel, or do not believe in modern medicine. Further, a selection of specimen sampling in favor of patients with obviously malignant breast tumor is possible; some early cases may have been missed. The time from specimen fixation to its examination was highly variable due to transportation issues; consequently, the quality of the immunohistochemistry was limited. This may have resulted in false-negative diagnosis of hormone receptor expression, even though our results show a relatively high proportion of hormone receptor-negative disease which is possibly even higher [26]. After beginning of Tamoxifen donation in 2013, various logistic obstacles led to nonuptake, treatment interruptions and drop-out. Patients received standard daily treatment for < 2 years; therefore the influence of endocrine therapy on survival is probably minimal.

We see that establishment of a reliable decentralized pathology service and hormone receptor testing is crucial to any oncologic treatment center. In line with the Breast Health Global Initiative guidelines for low-resource settings, we suggest oophorectomy in premenopausal women or alternatively the administration of endocrine treatment [36]. Since 65.7% of the patients of this study population show endocrine responsiveness, one measure to achieve a relative reduction of mortality of 34% [37] would be to consequently administer Tamoxifen to all women, also with hormone receptor unknown disease. It is an inexpensive, safe, effective, and easy to distribute systemic therapy which is available in Ethiopia. The adherence, efficacy, and side effects need to be investigated in more detail in Sub-Saharan Africa. The long time lapse to presentation to seek medical advice after the onset of the first symptoms highlights the need to implement measures of building awareness, early detection, and downstaging. Downstaging programs could be integrated into the existing structures like the Ethiopian Health-Extension program. The possible benefit of downstaging programs in low-resource countries has been assessed in multiple studies [38–41].

Conclusion

Patients with operated BC in a rural hospital in Western Ethiopia with nearly no access to adjuvant therapy had mainly hormone receptor-positive disease; they present at advanced stage and had an overall survival of only 53% after 2 years. Especially, patients with clinically positive lymph nodes, tumors staged cT3 or cT4 and hormone receptor-negative disease had an unfavorable prognosis. The establishment of a reliable pathology service as well as receptor testing and securing adjuvant therapy (e.g., tamoxifen) is crucial to assure adequate diagnosis and treatment of breast cancer patients, and thereby improve quality of care and avert premature deaths in the region.

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Compliance with ethical standard

Conflict of interest The authors declare that they have no conflicts of interest.

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Breast cancer survival in Ethiopia: A cohort study of 1,070 women

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There is little information on breast cancer (BC) survival in Ethiopia and other parts of sub-Saharan Africa. Our study estimated cumulative probabilities of distant metastasis-free survival (MFS) in patients at Addis Ababa (AA) University Radiotherapy Center, the only public oncologic institution in Ethiopia. We analyzed 1,070 females with BC stage 1–3 seen in 2005–2010. Patients underwent regular follow-up; estrogen receptor-positive and -unknown patients received free endocrine treatment (an independent project funded by AstraZeneca Ltd. and facilitated by the Axios Foundation). The primary endpoint was distant metastasis. Sensitivity analysis (worst-case scenario) assumed that patients with incomplete follow-up had events 3 months after the last appointment. The median age was 43.0 (20–88) years. The median tumor size was 4.96 cm [standard deviation (SD) 2.81 cm; $n = 709$ information available]. Stages 1, 2 and 3 represented 4, 25 and 71%, respectively ($n = 644$). Ductal carcinoma predominated (79.2%, $n = 1,070$) as well as grade 2 tumors (57%, $n = 509$). Median follow-up was 23.1 (0–65.6) months, during which 285 women developed metastases. MFS after 2 years was 74% (69–79%), declining to 59% (53–64%) in the worst-case scenario. Patients with early stage (1–2) showed better MFS than patients with stage 3 (85 and 66%, respectively). The 5-year MFS was 72% for stages 1 and 2 and 33% for stage 3. We present a first overview on MFS in a large cohort of female BC patients (1,070 patients) from sub-Saharan Africa. Young age and advanced stage were associated with poor outcome.

Epidemiology

Key words: breast neoplasms, Africa, Ethiopia, survival, prognosis

Abbreviations: AA: Addis Ababa; AC: adriamycin cyclophosphamide; BC: breast cancer; BHGI: Breast Health Global Initiative; c: clinical; CI: confidence interval; DAG: directed acyclic graphs; FAC: 5-fluorouracil, adriamycin, cyclophosphamide; DALY: disability adjusted life year; HR: hazard ratio; LN: lymph nodes; M: distant metastasis; MFS: distant metastasis-free survival; N: nodal status; NOS: not otherwise specified; p: pathological; SD: standard deviation; T: tumor size

Additional Supporting Information may be found in the online version of this article

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Ethiopia is the second most populated country in sub-Saharan Africa.[1] In 2012, Ethiopia reported a population of 86.6 million people (estimated in 2013); nearly half (47%) was under the age of 15 years and life expectancy was 58 years. Ethiopia is one of the most rural countries in the world, with only 17% of the population living in urban areas. Ethiopia is a very diverse country, covering 80 different ethnic groups. The gross national income per capita was $870 in 2008; the per capita total expenditure on health was $30 (10% of total government expenditures) in 2007.[2] The centrally located capital of Ethiopia, Addis Ababa (AA), is a fast growing city with a radical change in lifestyle: the total fertility rate is only 1.5 as opposed to 5.5 children per women in rural Ethiopia. There are around 122 public and about 50 private hospitals in Ethiopia; this is 1:671,402 population.[3] One striking problem compared with other countries of sub-Saharan Africa is the scarcity of medical personnel, *e.g.*, only 0.4 physicians per 10,000 inhabitants compared with five times more physicians on average in the African region. The prevalence of HIV is still low around 2% (2.1%). Communicable diseases are still the major burden of disease as a

What's new?

There is little information on breast cancer survival in Ethiopia and other parts of sub-Saharan Africa. This study is the first to report on outcome of a large cohort of sub-Saharan patients with newly diagnosed breast cancer receiving standardized therapy in the only oncologic referral center in Ethiopia. Based on 1,070 patients with a median follow-up of 23 months, the study found a distant metastasis-free survival (MFS) after 2 years of 74% - a rather favorable outcome considering the limited resources. The effect of potential determinants on MFS was estimated, with young age and advanced stage both associated with poor outcome.

percentage of total disability-adjusted life years (DALYs) (73%).[4] Similar to other developing countries, non-communicable diseases are emerging. Breast cancer (BC) has now become the most commonly diagnosed cancer in women in several sub-Saharan African countries. This is a shift from previous decades when cervical cancer was the most commonly diagnosed cancer.[5] Furthermore, the burden of BC is likely to increase in the coming decades.[6] This probably reflects increases in the prevalence of known risk factors associated with urbanization.[6–8] In Ethiopia, an estimated age-standardized incidence rate of 19.5 per 100,000 and an estimated age-standardized death rate of 11.8 per 100,000 females are reported.[9] The World Health Organization (WHO) declared the fight against cancer a priority for all governments in 2005.[10] The Breast Health Global Initiative (BHGI) states that before any targeted national program in a specific country can be set up, data on the incidence and prognosis should be obtained.[11,12] A review of the literature revealed that only few data on BC survival from sub-Saharan Africa are available.[8]

Unlike the Western world, where women present early and have a good chance of survival, women in Ethiopia usually present late and are expected to have a very limited life span. Public oncologic treatment including radiotherapy in Ethiopia is limited to the Radiotherapy Center at AA University Hospital, staffed with four oncologists. Limited oncologic service (chemotherapy without radiotherapy) is offered by these oncologists in four private clinics. Breast surgery is offered at nearly all hospitals by general surgeons throughout the country. A system to supply patients without financial resources is in place for government hospitals ("poor-papers" to ensure free treatments are issued by local authorities). Since 2005, evidence-based standards of BC care have been adapted according to the BHGI.[13] Women with BC account for 19% of the total cancer patients. From 2006 through 2010, an independent project funded by AstraZeneca Ltd. (Cambridge, UK) and facilitated by the Axios Foundation (Paris, France) provided free endocrine treatment (tamoxifen and anastrozole) for estrogen receptor-positive and -unknown patients.[14] Information about the program was widely distributed amongst institutions, cancer organizations and mass media in AA. Because of this unique situation, we considered BC patients at the AA University Radiotherapy Center from 2006 to 2010 as a representative cohort of patients, presuming that the majority of patients found their way into the program and came for regular follow-up to receive their endocrine medication.

The primary aim of our study was to estimate distant metastasis-free survival (MFS) of women with BC diagnosed between June 1, 2005 and May 31, 2010 at the AA University Radiotherapy Center. Furthermore, we estimated the effect of potential determinants including age, stage of the disease and histologic type on MFS.

Material and Methods

Women with a histologically verified primary diagnosis of invasive carcinoma of the breast [International Classification of Disease-Oncology (ICD-O-3) codes C50.0–9] without evidence of distant metastasis consulting the Radiotherapy Department of AA University between June 1, 2005 and May 31, 2010 were included in our study (n = 1,070). All patient and tumor characteristics and information concerning therapy and outcome were documented from patients' files.

According to international coding standards for cancer registries,[15] the date of incidence was defined as the first consultation at a hospital for the cancer in question. Information on tumor size (T) and nodal status (N) was used to derive stage by the American Joint Committee on Cancer staging system AJCC (seventh edition)[16]: stage 1 (TxN0); stage 2 (T0N1, T1N1, T2N0, T2N1 or T3N0) and stage 3 (TxN2, T3N1, T4Nx or TxN3). All staging information mentioned within the first 3 months after primary diagnosis was used. T-stage was assessed according to the 2009 TNM classification.[17] For N-stage, the information on involved lymph nodes (LNs) from the pathologist was used, given that an adequate number of LNs was examined (≥double the number of involved nodes for N1 and any number for N2 or N3). This information was used to derive the stage (UICC) as a potential prognostic factor for estimation of MFS-probabilities. Additionally, in patients without operation (n = 140) or neoadjuvant chemotherapy (n = 42), we decided to use clinical TNM to derive the stage (UICC) as a potential prognostic factor for estimation of MFS-probabilities. As these patients had T3 and T4 tumors, we assumed that clinical TNM would not differ from theoretical pathologic TNM. For patient characteristics, any positive LNs described in the pathology report and clinically detected suspect LNs were coded N+. Contralateral regional LNs clinically noticeable without evidence of a local contralateral disease were considered to be distant metastasis (M). M-stage: in low-resource settings,

standardized staging by imaging is often not done. In this cohort, a minimum of chest X-ray and abdominal ultrasound were usually performed. A lack of clinical symptoms (n = 149) or radiologically confirmed absence of distant metastasis (n = 921 investigated with chest X-ray and abdominal ultrasound) at diagnosis was considered to be free of distant metastasis. Bone scans were not available. Tumor histology was classified according to written notes from pathology reports as ductal not otherwise specified (NOS) or lobular, and all others were summarized as other/unspecified.

The primary endpoint of our study was MFS because mortality data could not be obtained (patients usually die at home, so no death registration is available). Person time equaled the time from the date of diagnosis to the date of distant metastasis or to the date of last contact. Women without event were right-censored at the last visit to the clinic. Information was collected between October 14, 2010 and the closing date March 23, 2011. All patients who had not come for their appointment since more than 6 months ago were considered to have incomplete follow-up. Different patterns in right-censoring for incomplete follow-up over time were investigated between established prognostic groups of interest (in our case, information on age, stage and histology was available). No differences were seen using a Cox model to determine hazard ratios (HRs) for incomplete follow-up among the prognostic groups. During follow-up, patients were investigated for clinical signs of metastasis. M was confirmed by positive findings on imaging or pathologic diagnosis [two cases (0.7%) out of 285 were diagnosed by strong clinical suspicion only]. The time of occurrence of distant metastasis was defined as the time point of a positive finding on imaging or of a strong suspicion of distant metastasis by clinical signs whichever came first. Local recurrence during follow-up time was not analyzed, because operation notes and pathology reports did not sufficiently report about remaining tumor and surgical margins. Therefore, primary progression and local recurrence could not be precisely distinguished. Of 372 patients who showed local tumor after surgery, 163 also developed distant metastasis. Of 16 patients who were known to be certified dead, 15 died of BC. Only one of 16 patients died of a cause unrelated to BC; this patient was right-censored.

Analyses were done with SAS® (SAS, Cary, NC), Version 9.3. Median follow-up time was 23.1 (0–65.6) months. We estimated MFS by means of Kaplan–Meier survival analysis. We used causal graphs [directed acyclic graphs (DAGs)] to identify confounding factors.[18] Minimally sufficient adjustment sets were calculated (Supporting Information 1) using a standard software program.[19] Adjustment for age was done for stage and histology. We used crude and multivariable Cox proportional hazards regression to estimate unadjusted and adjusted HRs and corresponding 95% confidence intervals (95% CIs) with respect to prognostic factors. We checked the assumption of proportional hazards by the use of Schoenfeld residual plots.[20] Worst-case analysis considered all patients with incomplete follow-up as having developed distant metastasis 3 months after the last visit.

Ethical approval for our study was obtained from Institutional Review Boards of AA University Medical Faculty and Martin Luther University Halle. The study was conducted without individual informed consent as the study relied on retrospective data collected as part of routine patient care.

Results

Of 2,031 registered patients, 1,507 files could be retrieved. Overall, 1,070 women fulfilled the inclusion criteria (Supporting Information 2). Nearly all patients (n = 930; 87%) received an operation. The majority had modified radical mastectomy (n = 880; 95%). Of these, an estimated 20% were operated at the Department of Surgery at AA University Hospital. In 628 surgery reports describing the margins, 69.9% reported surgical margins free of disease and 30.1% had margins involvement [for 302 patients (32%), no information on margins was available]. The majority of patients (n = 893; 83%) also received chemotherapy, mainly anthracycline-containing chemotherapy (n = 782). Of these, about 70% were administered at the AA University Radiotherapy Center. The preferred anthracycline-containing regimen was FAC (5-fluorouracil 500 mg/m^2, adriamycin 50 mg/m^2 and cyclophosphamide 500 mg/m^2) for 666 patients, AC (cyclophosphamide 600 mg/m^2 and adriamycin 60 mg/m^2) for 116 patients and for 76 patients cyclophosphamide, methotrexate and 5-fluorouracil (CMF) was used. Taxanes were not available in general. Of all chemotherapy patients, 753 patients (83.7%) received a full six cycles of chemotherapy, mainly FAC (n = 577). There were 42 patients who received neoadjuvant chemotherapy. All endocrine therapy for positive or unknown receptor status (n = 864) was administered at the AA University Radiotherapy Center. Patients' everyday compliance to endocrine treatment could not be assessed. Adjuvant treatment (if applied) was given rather well-timed; 79% of patients with chemotherapy started within 6 months and 77% of patients with endocrine therapy started treatment within 12 months after surgery.

In 285 women (26.6%), distant metastasis occurred during follow-up. The majority of women came for regular follow-up visits ranging from 8.1 to 65.6 months after primary diagnosis (median 23.1 months). Altogether, 101 women (9.4%) did not have any follow-up visit (after completion of therapy: maximum 8 months after the date of diagnosis) and 130 women (12.1%) had incomplete follow-up later on. At the end of the study, 78% of women had complete follow-up.

The age of the women ranged from 20 to 88 years (median age 43.0 years), with women aged 30–39 being the largest group of the study population (37.9%). Almost half of the women were premenopausal (49.7%; n = 889 information available). Among the women whose origin had been specifically inquired when their history was taken, half were classified as AA and half as non-AA. The majority of women presented with stage 3 disease. Nodal status was positive in

Table 1. Clinical and pathological characteristics of the patients

Characteristic	Number	Proportion (%)	At the end of the study—Proportions within different prognostic groups					
			Complete follow-up (metastasis)	(%)	Complete follow-up (without disease)	(%)	Incomplete follow-up	(%)
Total population	1,070	100.0	285	26.6	554	51.8	231	21.6
Place of origin								
Addis Ababa	521	53.5	139	26.7	287	55.1	95	18.2
Non-Addis Ababa	453	46.5	123	27.2	217	47.9	113	24.9
Age (years)								
<30	145	13.6	51	35.2	56	38.6	38	26.2
30–39	406	37.9	122	30	204	50.2	80	19.7
40–49	274	25.6	71	25.9	141	51.5	62	22.6
50–59	161	15.1	26	16.1	102	63.4	33	20.5
≥60	84	7.9	15	17.9	51	60.7	18	21.4
Menopausal status								
Premenopausal	442	49.7	143	32.4	211	47.7	88	19.9
Postmenopausal	447	50.3	97	21.7	243	54.4	107	23.9
Stage (UICC)								
1	25	3.9	4	16	17	68.0	4	16.0
2	163	25.3	23	14.1	106	65.0	34	20.9
3	456	70.8	154	33.8	185	40.6	117	25.7
Nodal status								
Positive	632	80.8	177	28	317	50.2	138	21.8
Negative	150	19.2	25	16.7	93	62.0	32	21.3
Histology								
Ductal not otherwise specified	811	79.2	198	24.4	455	56.1	158	19.5
Lobular	55	5.1	18	32.7	23	41.8	14	25.5
Other/unspecified	204	15.7	69	33.8	76	37.3	59	28.9
Grade								
1	92	18.0	16	17.4	56	60.9	20	21.7
2	291	57.2	68	23.4	175	60.1	48	16.5
3	126	24.8	35	27.8	67	53.2	24	19.0
Surgery within 6 months	902	97.0	220	24.4	504	55.9	178	19.7
Chemotherapy within 6 months	706	79.1	173	24.5	398	56.4	135	19.1
Endocrine therapy within 12 months	665	76.7	138	20.8	432	65.0	95	14.3
Tumor size (mean, standard deviation)	4.96 ± 2.81 cm							

81% of cases. The most frequent histological type of BC was ductal carcinoma NOS. About half of the women had a pathology report showing grade 2. The extent of incomplete follow-up and differences in distribution by prognostic factors are shown in Table 1.

MFS of patients after 2 and 5 years was 74 and 46%, respectively. In our worst-case analysis, MFS declined to 59 and 27%, respectively (Fig. 1). The difference between documented results and worst-case analysis was less than 20% for 2- and 5-year MFS (Table 2).

To find out the factors influencing MFS, HRs were calculated for the different patient characteristics (Fig. 2). Differences between unadjusted and adjusted values can be seen in Supporting Information 3. MFS was highest in women aged 50–59 years and was lower in younger age groups (Fig. 3). Women aged 60 years and above also tended to have worse

prognosis compared with those aged 50–59 years. The HR for distant metastasis of patients <30 years of age was higher (HR = 3.20, 95% CI 1.99–5.14) compared with that of women aged 50–59 years (Fig. 2).

Women with stage 3 disease had a considerably worse MFS than patients with stage 1/2 disease, showing an HR of 2.62 (Fig. 2). Women with unknown stage had MFS between those with stages 1/2 and stage 3 (Fig. 4).

Tumor histology was grouped as ductal NOS, lobular and other/unspecified (*e.g.*, four phyllodes tumors, two sarcomas and medullary carcinoma). Patients with ductal histology had the best MFS compared with the other entities. The lobular group also included specified lobular cancers; outcome was not as beneficial as expected for pure lobular cancers (Supporting Information 4).

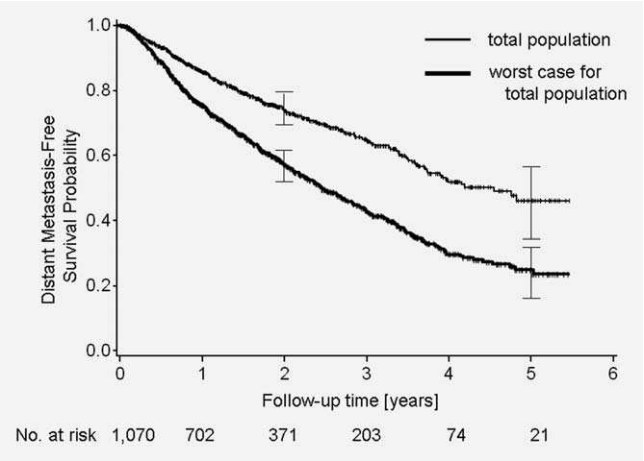

Figure 1. Kaplan–Meier plot of cumulative distant metastasis-free survival is shown as recorded and as worst-case scenario assuming that patients not remaining in care (had not visited for >6 months) had incomplete follow-up. All patients with incomplete follow-up were considered to have distant metastasis 3 months after their last visit.

Discussion

This is the first detailed and largest study on BC survival in Ethiopia and other parts of sub-Saharan Africa. Overall, MFS probability in this cohort of Ethiopian women with BC was 74% after 2 years and 46% after 5 years [median follow-up 23.1 (0–65.6) months]. Patient characteristics in our cohort tended to be unfavorable compared with Western cohorts; more than 50% were premenopausal, aged <40 years and/or with stage 3 disease. Tumor biology was more favorable; the majority was ductal and grade 2. Often cancer survival data in developing countries have the endpoint of overall survival. We only found follow-up data with an endpoint on MFS from Nigeria, without any information on treatment. Out of the described 308 cases from Nigeria, 106 cases with incomplete follow-up were omitted and only 202 were entered into Kaplan–Meier plots. The plot shows only those patients who developed metastasis within 5 years; therefore, a comparison

Table 2. Distant metastasis-free survival (MFS) probabilities (in %)

Prognostic factor	Main analysis		Worst-case analysis	
MFS (95% CI)	**After 2 years**	**After 5 years**	**After 2 years**	**After 5 years**
All patients	74 (69–79)	46 (35–58)	59 (53–64)	27 (19–35)
Place of origin				
Addis Ababa	74 (66–81)	43 (26–60)	61 (53–69)	27 (15–41)
Non-Addis Ababa	73 (65–80)	49 (33–64)	54 (46–63)	26 (16–38)
Unknown	79 (63–91)	57 (29–83)	67 (50–82)	31 (12–55)
Age (years)				
<30	72 (57–85)	13 (0–58)	48 (33–64)	7 (0–33)
30–39	70 (61–78)	43 (24–63)	57 (48–66)	25 (13–40)
40–49	71 (59–81)	46 (25–68)	56 (45–66)	26 (13–43)
50–59	88 (77–95)	67 (45–85)	72 (59–83)	46 (29–64)
≥60	86 (71–96)	64 (35–89)	71 (53–87)	32 (8–62)
Stage (UICC)				
1–2	85 (74–93)	72 (52–88)	71 (59–82)	40 (19–64)
3	66 (57–74)	33 (16–53)	48 (40–57)	16 (7–28)
Unknown	78 (70–85)	49 (31–66)	65 (57–74)	33 (21–48)
Histology				
Ductal not otherwise specified	77 (71–82)	49 (36–63)	64 (58–70)	30 (20–40)
Lobular	63 (37–85)	42 (11–77)	44 (22–68)	24 (5–52)
Other/unspecified	61 (46–76)	28 (8–54)	40 (28–54)	14 (3–30)

Abbreviation: CI: confidence interval.

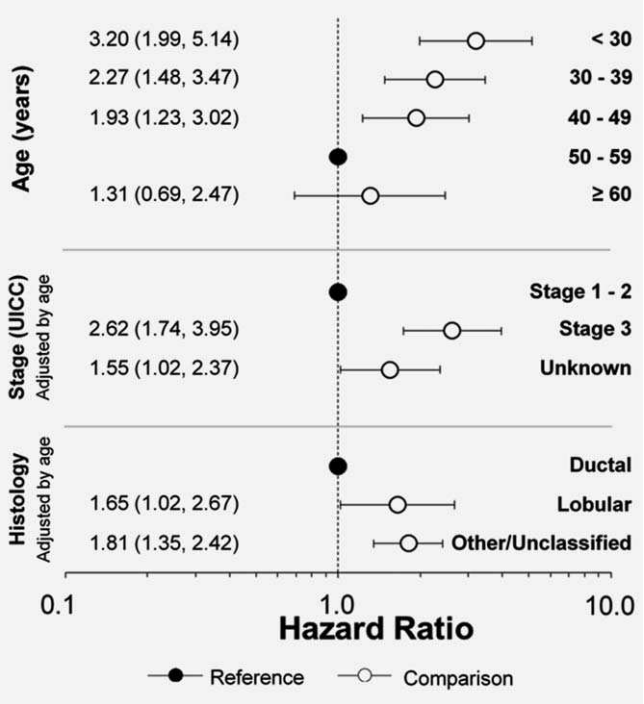

Figure 2. Hazard ratios for patients with different prognostic factors. [mean (95% CI)]

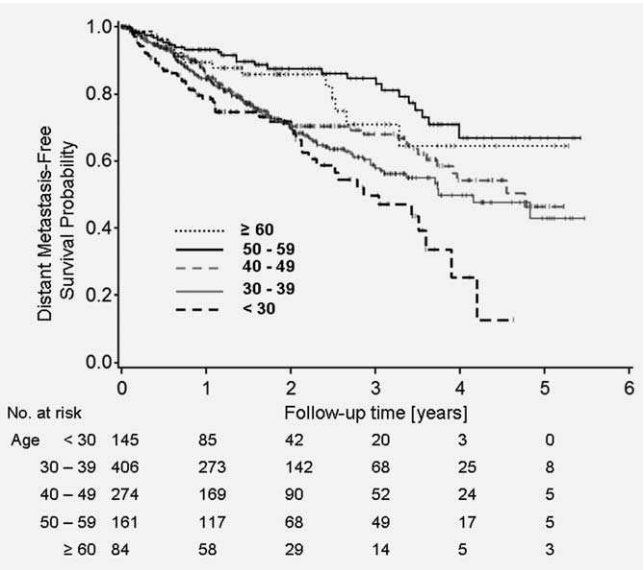

Figure 3. Kaplan–Meier plot of crude cumulative distant metastasis-free survival probabilities is shown according to age at diagnosis. Women were stratified into 10-year age groups.

is not possible.[21] Looking at worldwide 5-year overall survival probabilities, the figures ranged from 89.2% in highly developed countries down to 38.8% in Algeria and 12% in The Gambia.[22,23] A report from Uganda showed an overall survival probability for stage 1–2 cancers of 74% and stage 3–4 cancers of 39%.[24] Our stage 1 and 2 patients showed 72% and stage 3 patients showed 32% MFS probability, and overall survival is expected to be higher. This possibly points to a more favorable outcome in our cohort from Ethiopia.

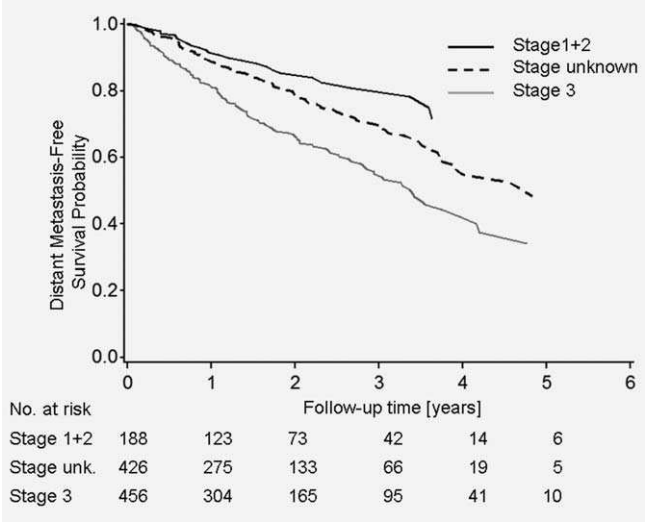

Figure 4. Adjusted cumulative distant metastasis-free survival probabilities is shown according to stage at diagnosis. Patients were classified according to UICC stages (adjusted according to age) (unk.: unknown).

The median age of 43 years (20–88) in our cohort was slightly lower compared with studies from other countries. A previous study conducted from 1995 through 1999 on 125 consecutive BC cases from AA University Hospital also revealed a median age of only 40 years.[25] Reports show a median age of 46 years in Mali ($n = 118$), 46 years in Tanzania ($n = 328$), 49 years in Ghana ($n = 330$) and 48 years in Nigeria ($n = 192$).[26–29] The differences in MFS in our age groups point to a possibly favorable prognosis in women between 50 and 59 years of age in terms of MFS. This is similar to Western studies showing that younger women have worse outcome.[30] It is most likely that general health status is responsible for the suboptimal therapy and tendency for poorer MFS in our group of women aged 60 years or more.

As in other developing countries, a large proportion of women presented with a late stage of the disease (70% stage 3). This finding is in line with previous studies from Africa. For example, the study from Tanzania reported that 71% of patients with nonmetastatic BC were stage 3.[31] The study from Uganda reported that 69% of the women had stage 3 BC.[24] In Egypt, 60% of women presented with late-stage disease in a prospective study.[32] In contrast, the North American Surveillance, Epidemiology, and End Results Program database reveals that 60% of BCs are diagnosed at stages 1 and 2.[30] In our study, stage 3 BC patients showed an HR of more than 2.5 compared with the MFS in stage 1/2 patients. This highlights the fact that earlier detection would indeed improve outcome in BC patients in Ethiopia.

Often, tumors in the African setting are described as aggressive with high grading. Ly *et al.* reported a high incidence of grade 3 tumors (78%) from Mali.[26] In Ghana, 54% were grade 3.[28] In Tanzania, 56% grade 3 cases were seen.[27]

In Nigeria, the findings are contradictory: Huo *et al.* found 44% grade 3 tumors,[33] whereas Adebamowo *et al.* found only 22% grade 3 tumors.[29] Such high-grade tumors occurred less frequently in our cohort (35%). Because of the subjective nature of the assessment, a degree of uncertainty must be taken into account. Altogether, these findings may reflect a less aggressive nature of tumors from Ethiopia.

We found that the majority of patients received adjuvant treatment according to the BHGI guidelines, which recommend anthracyclines (782 of 893 patients with chemotherapy received anthracyclines) and tamoxifen (for positive and unknown hormone receptor status) for this setting with limited resources.[13] Adjuvant therapy was done in a standardized manner at the AA University Radiotherapy Center for the majority of patients. Surgery was mainly modified radical mastectomy (880 of 930 operated patients). The fact that nearly 80% of surgery was done in peripheral hospitals might account for a suboptimal standard. There are published data about the adequacy of surgery in peripheral hospitals from India. Thorat *et al.* reported that out of 424 referred cases, 153 were reoperated owing to clinically suspected inadequate removal of tumor.[34] Of those, 64 patients were diagnosed with additional involved LNs; no tumor was found in the remaining breast tissue. Therefore, in our cohort from a similar setting, there might be a considerable proportion of patients with involved LNs in situ. This could explain the high number of local recurrences seen. Additionally, there were 140 patients who did not receive any surgery owing to a lack of plastic surgery options. These patients did receive chemotherapy. Altogether, our cohort consisted of about 700 patients who received optimal care with mastectomy, anthracyclines and endocrine treatment. As we wanted to focus on a consecutive cohort in this setting with limited resources, we decided to describe the total cohort including the group of patients with inadequate treatment. The reasons for different BC-specific survival of ethnic groups are unknown. Among US citizens, Caucasian women have the best, African-American women have poorest and other immigrants have intermediate BC-specific survival.[35] Possible factors that contribute to these differences are unfavorable stage at diagnosis, limited access to care, comorbidities, socioeconomic status, obesity and physical activity. Besides genetic factors leading to differences in tumor biology, patient and lifestyle factors might also contribute to the differences in findings. Women of African origin have a much more diverse genetic background than Caucasian women.[36] In addition, the environment and lifestyle differ considerably throughout the African continent.[37] We hypothesize that East African women have better survival outcome than West African women (Gambia, Nigeria) because of more favorable biological characteristics such as tumors with a lower grade. In addition, in Ethiopia the predominantly rural environment (*e.g.*, less processed food) and non-Westernized lifestyle (*e.g.*, underweight, high physical activity, high number of children, long period of breastfeeding, less hormonal contraceptives or replacement therapy) may reflect differences from other African countries. Also, the lack of awareness, low economic status, lack of knowledge, *etc.* may result in less treatment uptake and therefore patient selection.[38]

There are some factors that limit our results. First, the non-AA population (97% of Ethiopia) was most likely underrepresented at the AA University Radiotherapy Center. We found that non-AA women tended to be younger, to have a higher stage of disease, less frequent endocrine treatment (differences of up to 6% between groups) and similar MFS. These might be general features of the disease in the rural setting or might be the result of patient selection. Because of the rather high costs of living in the capital city AA, we have to assume that patients with low income, probably mostly from rural areas, may not reach the AA University Radiotherapy Center. Therefore, this cohort is probably exclusive of very poor patients, especially those living further away. It is possible that this group that hardly accesses the health care system would present late, have less compliance, not remain in care and therefore add to the unfavorable higher stage group with reduced probabilities. Second, information on stage was missing in about 40% of the cases. As the MFS of patients with missing stage was between that of patients with stage 1/2 and stage 3 disease, these patients most likely reflected a mixture of patients from the other two groups. Third, about 25% of the registered files were not found. The record system at the AA University Radiotherapy Center is based on hard copy patient files that are stored according to names and patient numbers. Files can easily be misplaced. Illiteracy frequently results in various spellings of names; files are frequently not found. We are not aware of any other reason for missing files and therefore do not suspect a selection bias through this fact. Fourth, our cohort showed a considerable proportion of women with incomplete follow-up (21%). Therefore, the assumption of right-censoring being independent of time to distant metastasis may not be valid. By analyzing the time pattern of right-censoring in incomplete follow-up patients within prognostic groups, we found no differences between prognostic groups. However, this does not prove the above-mentioned assumption of independence for the prognostic factors. In a setting without valid endpoints like vital registration and with a retrospective design, these doubts cannot be ruled out. For sensitivity analysis, all patients with incomplete follow-up were considered to develop distant metastasis 3 months after their last appointment. The resulting differences in MFS did not differ among the subgroups of the prognostic factors of interest. Therefore, we believe that potential bias was not substantial, although we are aware that these observations cannot exclude that right-censoring was related to the risk of distant metastasis.

We reported data from 1,070 women with BC stage 1–3 followed for a median time of 23.1 (0–65.6) months. These women showed a rather favorable 5-year outcome of 45% MFS compared with previously described smaller cohorts from sub-Sahara Africa in the literature. We found a lower

median age and a higher proportion of grade 2 tumors in our cohort compared with those previously described in other parts of sub-Saharan Africa, mainly in West-Africa (older patients, more grade 3). In our cohort, outcome was negatively influenced by age below 49 years and age above 60 years, higher stage at presentation and a histology other than ductal carcinoma NOS. These findings are in line with published data from Caucasian patients. The majority of women who presented with stage 3 disease at diagnosis had worse outcome than stage 2 patients. This shows the potential benefit and urgent need of downstaging programs, which have been proven successful in similar settings elsewhere.[39]

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9 Selbstständigkeitserklärung

Ich erkläre hiermit, die Arbeit selbständig geschrieben und keine anderen als die angegebenen Quellen benutzt zu haben.

5.12.2018
Date

Dr. Eva Johanna Kantelhardt geborene Ulbrich

10 Erklärung über frühere Habilitationsversuche

Diese Arbeit habe ist mein erster Habilitationsversuch. Ich habe diese Arbeit ausschließlich an der Medizinischen Fakultät der Martin-Luther-Universität Halle-Wittenberg als Habilitationsschrift eingereicht.

5.12.2018
Date

Dr. Eva Johanna Kantelhardt geborene Ulbrich

11 Curriculum vitae

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Institution	Klinik und Poliklinik für Gynäkologie
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Studium und Beruflicher Werdegang

1992 – 1999	Humanmedizin an der Georg August-Universität Göttingen
1994 – 1999	Promotion: „*Zucht und Analyse von Mäusen mit einer Defizienz der beiden Mannose-6 Phosphat-Rezeptoren*“, Betreuer: Prof. Dr. Kurt von Figura
Januar 2000	Promotion zum Dr. med., Gesamturteil: sehr gut
Seit 6.1.2000	Ärztin bzw. Fachärztin Klinik und Poliklinik für Gynäkologie, Martin-Luther-Universität Halle-Wittenberg
2005	neun Monate Rotation Forschungslabor Klinik f. Gynäkologie (Prof. Dittmer)
2013 – 2015	zwei Jahre wissenschaftliche Rotationsstelle
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Seit 1.7.2015	Geteilte Stelle als Fachärztin an der Klinik und Poliklinik für Gynäkologie und Wissenschaftlerin am Institut für Medizinische Epidemiologie, Biometrie und Informatik

Elternzeiten: 4.5.2008 – 3.5.2009; 15.10.2010 – 30.9.2011; 3.10.2015 – 31.8.2016

Studienleitungen

1) 2009 – 2012 “PiA: Prognose im Alltag“: Patientinnen mit operablem Mammakarzinom – Vergleich der Invasionsfaktoren uPA/PAI-1 mit anderen Prognosefaktoren. Eine prospektive, multizentrische, nicht-interventionelle Beobachtungsstudie (n=1046) Zusammenstellung von Daten und Gewebe (gefroren und Formalin-fixiert) einer konsekutiven, repräsentativen Kohorte von Patientinnen mit operablem Mammakarzinom aus sechs zertifizierten Brustzentren in Deutschland.

2) 2014 – 2016 „Breast Cancer Biology in Africa”: Sammlung von Formalin-fixierten Blöcken von konsekutiven Patientinnen mit Mammakarzinom aus 10 Krankenhäusern in 7 afrikanischen Ländern (n=706).

3) 2016 – jetzt „Stage, Therapy and Outcome in Africa“: Dokumentation von Stadien, Therapie und Überleben von je 300 Patientinnen (Mamma, Zervix, Prostata, Kolo-Rektum und NHL) aus 10 populations-bezogenen afrikanischen Krebsregistern

Erfahrungen: Doktoranden Co-Betreuung in den Arbeitsgruppen Gynäkologie (Prof. Thomssen) und Epidemiologie (Prof. Stang und Prof. Mikolajczyk)

Afrika-Themen: 8 abgeschlossene Verfahren, 1 eingereicht, 13 Datensammlung beendet; derzeit Co-Betreuung der Datensammlung von 8 deutschen und 7 äthiopischen Doktoranden in Halle & Addis Ababa.

Klinische Themen Gynäkologie: 2 abgeschlossene Verfahren, 4 Datensammlung beendet; derzeit Co-Betreuung der Datensammlung von 2 Doktoranden.

5.12.2018

Datum Dr. Eva Johanna Kantelhardt geborene Ulbrich

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