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Establishing an Ethiopian Breast Cancer Registry: First Step Toward Improved Cancer Control

By

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Degree to be awarded: Master of Public Health (MPH)

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Abstract

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By Timothy P. Love, MD

BACKGROUND: Breast cancer is the most common cancer in women and a leading cause of death and disability worldwide. Breast cancer in Ethiopia represents a major clinical problem but understanding the true scope of the problem will require enhanced breast cancer epidemiology. The purpose of this study was to determine the feasibility of establishing tumor registries in Ethiopia, starting initially with breast cancer cases treated at four hospitals in Ethiopia.

METHODS: Newly diagnosed breast cancers were retrospectively registered, using existing clinical data, with incidence dates ranging from September 2005 to March 2013. Patient demographics, medical information, tumor characteristics, treatment modalities, and outcome data were all input into a formal open source cancer registry software program (CanReg5, IARC) and subsequently analyzed using a separate statistical analysis software package (SAS 9.3).

RESULTS: Preliminary data from 318 patients were analyzed. Patients were 94.3% female with a mean age of 41.3 years (median age: 40; range: 16-80 yrs). Average time from onset of symptoms to time of presentation was 15.0 months; 72.0% underwent pathologic evaluation. Cancer stage distribution was: Stage 0 - 0 (0%), Stage I - 17 (5.4%), Stage II - 75 (23.6%), Stage III - 170 (53.5%), and Stage IV - 56 (17.6%). Therapeutic modalities post-diagnosis included: surgery: 236 (74.2%); referral for chemotherapy 87 (27.4%) and radiation therapy 55 (17.3%); and endocrine therapy: 32 (10.1%).

CONCLUSION: Feasibility of developing cancer registries in Ethiopia was established. As expected in a country with no screening mammography program, the distribution of cancer stage was much later than observed in more resourced countries. Development of tumor registration is essential to accurately assess the scope and detail of breast cancer incidence, staging, and mortality in Ethiopia and other low- or middle-income countries. Registries will enable monitoring of cancer stage, treatment patterns, and outcomes and inform policies to design and evaluate programs of breast cancer prevention, diagnosis, and treatment. Barriers to effective registration include lack of documentation of clinical data; inadequate resources to support registries; and no trained registrars in Ethiopia. Strategies to address such barriers will be critical to improving quality of cancer care.

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And to my wife and son, Laura and Sam, I cannot imagine having done this without you and I thank God continually for your unflagging support. May this be but a small part of our grand adventure together!

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CHAPTER 1: INTRODUCTION

Communicable diseases have represented the greatest threat to human health over much of the history of medicine and composed the vast majority of the global burden of disease. However, that time has now passed. The epidemiological transition, as described by Abdel Omran, is already well underway across the globe (Omran, 1971). The World Health Organization (WHO) recently declared that the year 2008 was one in which an estimated 36 million, or 63%, of the 57 million global deaths were due to noncommunicable diseases (NCDs), nearly 80% of this burden being borne by low- and middle-income countries (LMICs) (World Health Organization, 2011). NCDs are those diseases and conditions which are non-infectious and not transmissible among people, most commonly meant to include diabetes, cardiovascular disease, chronic respiratory illnesses, and cancer, among many others. Unfortunately, global health agendas and development goals have largely lumped NCDs together into a category that has received relatively little attention, when compared to communicable diseases, and even less funding (Adams, Grey, Magrath, Miller, & Torode, 2010).

Cancer represents a global problem that is "neither rare anywhere in the world, nor mainly confined to high-resource countries" (Ferlay et al., 2010a). In the year 2008, cancer is estimated to have produced 12.7 million new cases, caused 7.6 million deaths, and resulted in the loss of 169.3 million years of healthy life worldwide (Ferlay et al., 2010a Soerjomataram et al., 2012). The world population in 2012 topped 7 billion and is projected by the United Nations to reach 8.3 billion by the year 2030 with the greatest effects of population growth and ageing to be experienced in LMICs (United Nations Population Division, 2010). The projected growth in cancer rates, however, is grossly disproportionate to the growth in population. Cancer incidence is expected to rise from 12.7 million new cases in 2008 to 20.3 million in 2030, while cancer-related deaths are projected to rise from 7.6 million in 2008 to 13.2 in 2030 (Bray, Jemal, Grey, Ferlay, & Forman, 2012). Predictions of the WHO for the year 2020 have 70%

of 16 million new cancer cases arising in LMICs and cancer rates in Africa increasing by 400% by roughly 2050 (Lingwood et al., 2008; Morris, 2003).

In 2008, the highest cancer incidence rates in men were found in Australia & New Zealand (Age-standardized rate (ASR) 356.8 per 100,000), Western Europe (ASR 335.3 per 100,000), North America (ASR 334 per 100,000), and Northern Europe (ASR 288.9 per 100,000), which is largely attributable to the high rates of prostate cancer in these regions (ASRs >80 per 100,000 in each region). In women, the highest incidence rates were similarly found in North America (ASR 274.4 per 100,000), Australia & New Zealand (ASR 276.4 per 100,000), Northern Europe (ASR 257.8 per 100,000), and Western Europe (ASR 250.5 per 100,000) due to the high rates of breast cancer (ASRs >75 per 100,000 in each region) (Ferlay et al., 2010a, 2010b). Each of these regions is composed of countries with either high or very high human development indices and are the setting in which the most progress has been seen in cancer control and treatment. However, as above, predictions for growth in cancer incidence in the near future have more than 70% of new cases arising in LMICs, which will necessitate a paradigm shift in how the world approaches cancer prevention, treatment, and control.

In addition to more commonly cited incidence and mortality rates, prevalence is a valuable metric that demonstrates all people alive with a diagnosis of cancer at a given point in time and includes both those with active disease as well as those who have been effectively treated, or cured, of the disease. Prevalence therefore combines new, or incident, cases of cancer as well as those who have been effectively treated for cancer and survived. Countries with the highest prevalence of cancer can be assumed to have both a high incidence of cancer as well as favorable survival which results in the accumulation of survivors. Earlier this year, Bray et al., of the International Agency for Research on Cancer, used available data to determine the limited duration prevalence of cancer for the 5-year period of 2004 to 2008, which includes all cancer cases diagnosed during that period and still alive at the end. They estimated that 28.8 million persons were living with cancer at the end of 2008. With 5.2 million cases, breast cancer was found to be by far the most prevalent cancer worldwide, followed by prostate cancer and colorectal cancer, each with approximately 3.2 million cases. In this study, the prevalence of each type of cancer was displayed geographically around the world and broken by level of human development. The human development index (HDI), a composite rating based on standard health, education, and income statistics, was used to stratify countries by level of development. While cervical cancer was the most prevalent cancer in many low-HDI countries in sub-Saharan Africa, breast cancer was the most prevalent cancer in Ethiopia. However, cancer prevalence was found to be much lower across low-HDI regions than it was in high-HDI regions. While very high human development areas only possess one-sixth of the world's population, they possess nearly one half of the prevalence burden (47.2%), which is partially due to increased life expectancy in high-HDI settings (increased risk of cancer in older age) and partially due to their ability to effectively treat and cure cancers (Bray, Ren, Masuyer, & Ferlay, 2013). These essential differences in life expectancy and the presence of effective cancer treatment modalities in low-HDI settings are expected to change in coming years, which is projected to significantly increase the burden of cancer in these regions. (See graphical and geographical representations in Figures 2 and 3, respectively, of Bray, Ren, Masuyer, & Ferlay, 2013 available at http://onlinelibrary.wiley.com/doi/10.1002/ijc.27711/abstract by subscription.)

In high-resource settings there has been steady and substantive progress toward decreasing cancer incidence and cancer-related mortality, so much so that many are now additionally focusing efforts on improving quality of life in cancer survivors and reducing cancer-related disability. The disability-adjusted life years (DALYs) metric is commonly used to express the summative burden of a given disease by adding together the years of life lost because of premature mortality (YLLs) and years of life lived with disability (YLDs) caused by that disease. As above, it has been estimated that 2008 was a year which saw the loss of an estimated 169.3 million years of healthy life due to cancer worldwide. The primary contributors to premature death and disability were lung, liver, breast, and stomach cancer. Breast cancer in particular was found to be a major contributor to the cancer burden across all levels of human development and in all world regions with the exception of eastern Asia. DALY rates can be further manipulated to calculate YLLs as a proportion of total DALYs, as they were in the study by Soerjomataram et al. With cancer, this calculation reflects the proportion of disease burden that is caused by premature death rather than survivors who go on to live with some form of disability. As might be expected, the YLL to DALY proportion was low in countries with very high human development indices and quite high in countries with low human development indices. In fact, sub-Saharan Africa was the continent with the highest YLL to DALY ratio (96%) while North America was the continent with the lowest (84%). Breast cancer was one of several cancers noted to have the greatest variation in proportions between very high and low HDI countries (63% vs. 90%) (Soerjomataram et al., 2012). This means that while breast cancer patients in high-HDI countries might have a reasonable hope of survival, a much greater proportion of those diagnosed in a low-HDI country like Ethiopia will readily succumb to the disease.

Many countries have benefited tremendously from the development of comprehensive national cancer control programs to address the burden of cancer among their population. The WHO, acknowledging the growing burden of cancer and the need for such programs, has published this definition: "A national cancer control programme is a public health programme designed to reduce the incidence and mortality of cancer and improve the quality of life of cancer patients in a particular country or state, through the systematic and equitable implementation of evidence-based strategies for prevention, early detection, treatment, and palliation, making the best use of available resources" (World Health Organization, 2002).

While a comprehensive cancer control program has many facets, the publication from the WHO and numerous others have outlined the crucial role that cancer surveillance and other epidemiologic studies must play in formulating the cancer control plan (Jensen et al., 1991; Olweny, 1985; Valsecchi & Steliarova-Foucher, 2008). Cancer surveillance has largely centered on the establishment of formal cancer registries over the past 60 years. Due to the complexity of cancer staging and the need for specialized data collection, sporadic and non-uniform cancer studies rarely yield much helpful information. Formal cancer registration continuously and systematically collects data about the personal characteristics of cancer patients in a given population and the clinical and pathologic characteristics of their cancers. Registry data are then able to be routinely analyzed and interpreted to provide a variety of statistics that illustrate the burden of cancer in a population. This information not only assists with further epidemiologic research, but serves as a foundation for the planning and evaluation of all health services involved in the prevention, diagnosis, and treatment of cancer. Some of the crucial functions of cancer registration and their role in the health system include:

- Baseline assessment of cancer incidence and mortality in a population;
- Assessment of differences in incidence and mortality that are indicative of inequality in prevention and care between and within countries or according to ethnicity, occupation, socioeconomic status, or area of residence;
- Monitoring of primary and secondary prevention campaigns' effect through trends in cancer frequency, survival, and stage distribution, or stage migration;
- Assessment of cancer treatment effectiveness based on survival trends;
- Development of cancer frequency projections that allow need-based planning of cancer services and prioritization of health system budgets and spending;
- Development of further epidemiologic investigations, such as causality studies, based on population findings and trends in risk factors (Dos Santos Silva & International Agency for Research on Cancer., 1999; Jedy-Agba et al., 2012; Jensen et al., 1991; D. M. Parkin, 2006; World Health Organization & International Agency for Research on Cancer, 2013a).

In Western, high-income countries such as the United States, cancer registries are present in most hospitals. These registries are typically under the leadership of an epidemiologist or physician trained in cancer surveillance and staffed by well-trained, certified cancer registrars who have completed significant coursework and training in cancer biology, cancer staging, data abstraction, and electronic data entry and database management. Every cancer patient diagnosed or treated at a hospital with a cancer registry would have their information abstracted by these registrars and enrolled in the hospital's registry. At regular intervals, hospital registries then upload these data to state, regional, and/or national cancer surveillance systems that track cancer statistics on a large scale.

Cancer epidemiology in African countries, particularly those in sub-Saharan Africa, remains poorly understood when compared to that which has been done in more resourced settings. The preponderance of cancer registries can be found in North America, Europe, and Australia, largely due to the level of economic and health system development that can be found in these countries. In North American and many European countries most patients diagnosed with cancer will be registered in a population-based cancer registry. About 11% of the population of Africa is covered by some sort of cancer registry and that 1% or less are covered by a true population-based cancer registry. While many LMICs may consider the establishment of cancer registries and the collection of basic cancer information to be a luxury, this health system activity has repeatedly been shown to be a cost-effective investment and the only legitimate method of determining the burden of cancer in a population (Valsecchi & Steliarova-Foucher, 2008; World Health Organization & International Agency for Research on Cancer, 2013a, 2013b).

Like many of its neighbors in sub-Saharan Africa, Ethiopia is a low-income country that suffers from very low levels of human development and a poorly performing health system. The United Nations Development Program uses the Human Development Index (HDI), previously described as a composite metric based on education, income, and health indicators, to rank countries on their level of development. In 2012, 186 countries were ranked and Ethiopia came in at 173rd, or in the bottom 7% (United Nations Development Programme, 2012). Similarly, the World Health Organization uses a standard collection of health indicators to rank countries' health systems based on performance and attainment of health goals. Out of 191 ranked health systems, the Ethiopian health system was 180th for overall health system performance, 186th for overall goal attainment, and 189th for health expenditure per capita (World Health

Organization, 2000). While these summary metrics may be nonspecific they give a good overview of the bleak situation that exists in Ethiopia.

Given the above, it is not surprising that Ethiopia is among the African countries with no existing population-based cancer registration or statistics. Though there is now a nascent effort to establish a population-based registry in the capital city, Addis Ababa, data remains forthcoming and all prior estimates of cancer incidence and mortality for the country have been based on either very small domestic studies or studies done in other countries. Established by the International Agency for Research on Cancer (IARC) and the WHO, the GLOBOCAN project is one of the foremost purveyors of contemporary cancer epidemiology in 184 countries, including Ethiopia. GLOBOCAN bases their cancer estimates on the most accurate data available for each country and mortality estimates for Ethiopia are based on two small domestic studies dating from 1987 and 1999 while incidence estimates are based entirely on studies from other countries, namely Sudan and Kenya (Ferlay et al., 2010b). Improved cancer epidemiology is desperately needed in Ethiopia to serve as the foundation for a national cancer control program and so that preparations may be made for the burgeoning burden of cancer in this country.

Purpose of Study

The primary purpose of this study is to determine the feasibility of establishing cancer registration in Ethiopia, starting with breast cancer. In so doing, we will be able to contribute to the current understanding of the cancer burden in Ethiopia. Through the establishment of formal institutional cancer registries and the training of cancer registrars, we have undertaken a cost-effective and sustainable, albeit small, step toward improved cancer control. What follows in this thesis will be a systematic review of cancer registration in low-resource settings in sub-Saharan Africa and an evaluation of the feasibility and acceptability of establishing breast cancer registries at selected sites in Ethiopia.

CHAPTER 2: LITERATURE REVIEW

Introduction

Reviewing literature that quantifies the cancer burden in Ethiopia reveals a great paucity of data, particularly with regard to breast cancer. Due to limited resources and a poorly functioning health system, very little has been done in Ethiopia to evaluate or address breast cancer and the studies which have been performed in Ethiopia, as discussed below, are often characterized by small samples sizes, very short study periods, imperfect methodology, and publication dates more than 10 years in the past. What follows is an overview of breast cancer in LMICs and Ethiopia, cancer registration, and literature describing the Ethiopian context in which this study was performed. For reference, the Appendix contains several maps in which the cities and regions mentioned below may be found

BREAST CANCER IN ETHIOPIA AND LMICS

The year 2010 was one in which the majority of the 425,000 breast cancer deaths reported worldwide did not occur in developed nations (211,000 deaths), but in developing nations (214,000 deaths) like Ethiopia (Anderson, 2012; Forouzanfar et al., 2011). GLOBOCAN estimates the incidence of breast cancer to range from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe. In Ethiopia, the incidence is estimated to be comparatively low at 19.5 per 100,000 (4935 cases) and an estimated mortality rate of 11.8 per 100,000 (2790 deaths), or more than half of incident cases (Ferlay et al., 2010a). As mentioned previously, these estimates for Ethiopia are largely based on studies that have been performed in other countries.

There have been few studies in the literature that make a passing reference to the prevalence of breast cancer in the Ethiopian population and even fewer studies designed to specifically address breast cancer in particular. One of the first of several similar studies to publish the relative prevalence of various neoplasms in the country was published by Aseffa et al. in 1986. This study reviewed 1,668 pathologic specimens collected between August 1981 and December 1984 in Northern Ethiopia at the Gondar College of Medical Sciences. Of the specimens reviewed, 446 (27.9%) were found to be neoplastic processes and of these, 243 (14.6%) were malignant. The three most frequent malignancies diagnosed were cervical cancer (12.8%), lymphomas (11.2%), and breast cancer (9.5%), with a comment that breast cancer diagnoses seemed to be becoming more frequent at that time. The authors conclude their discussion with a petition for the establishment of cancer registries and a system for following patients over time with cancer diagnoses (Aseffa, Ahmed Zein, & Stiehl, 1986).

A subsequent study by Loutfi and Pickering also published the relative frequency of cancers diagnosed at two pathology centers in Addis Ababa between 1979 and 1988. At the time of this study a total of four pathology centers existed for the whole country. The two centers from which they reported (Tikur Anbessa Hospital and the National Research Institute of Health) were the only centers serving the population of the capital city, which also happens to be the tertiary referral center for the country. A total of 4,067 cancer specimens were retrospectively reviewed with nearly twice as many cancer diagnoses for women as for men for each year reviewed (women: 396 cases/year vs. men: 219 cases/year). The most common cancer diagnosed among women was of the uterine cervix (32%), followed by breast cancer (23%) and ovarian cancer (7%). The most common cancer diagnosed among men was lymphoma (19%), followed by soft tissue sarcoma (13%) and head and neck cancer, which included thyroid cancer (11%). The frequency of breast cancer diagnosed among men was not mentioned. The authors additionally noted, from their data and other cited sources, that breast cancer ranks highly around the world and that population-based data are needed to calculate incidence rates and the true burden of disease in Ethiopia (Loutfi & Pickering, 1992). A similar retrospective review of 1,154 histologically verified cancer diagnoses was performed by Lindtjorn around the same time. Lindtjorn found the same three cancers, cervical, breast, and ovarian, to be the most common among women at the three hospitals he studied in Southern Ethiopia, a geographic region that happens to be quite close to Wolayita Soddo, one of the locations for this current study (Lindtjorn, 1987).

A more recent study by Bezabih (2004) reviewed all cytopathologic cancer diagnoses made in Jimma, Ethiopia between September 1998 and August 2002. All superficial malignancies amenable to the fine needle aspiration cytology (FNAC) biopsy technique were included in this study with the exclusion of all deep-seated neoplasms or malignancies. Over the four year study period, 3,200 FNAC biopsies were performed. Only 267 (8.3%) of these biopsies revealed malignant neoplasms, while the remaining 1,933 biopsies revealed some form of benign lesion. With 79 cases (29.6%), breast cancer was the most common of all malignancies found, followed by non-Hodgkin lymphoma (13.9%) and soft tissue sarcoma (9.7%). One third of patients found to have primary breast cancers in this study were also found to have ipsilateral axillary lymph node metastases at the time of FNAC, demonstrating the frequently late stage at diagnosis in this setting (Bezabih, 2004).

One of the only studies to investigate breast cancer epidemiology in Ethiopia exclusively was published by Gebremedhin and Shamebo (1998). The study is a review of 72 consecutive patients that were referred to the Hematology and Oncology Clinic of the central referral hospital, Tikur Anbessa Hospital (TAH), between January 1992 and December 1997. This cohort of 72 patients was composed of 57 patients referred from medical and surgical departments within TAH while 15 patients were actually referred from physicians abroad after receiving cancer care in another country, thus significantly limiting the generalizability of this study to the much poorer Ethiopian population. A range of demographic variables and tumor characteristics were collected from these patients and are summarized in Table 1 below.

This predominantly female cohort took approximately one year from the onset of breast-related symptoms to be diagnosed with breast cancer and demonstrated that the stage at diagnosis is much later than what was observed in high-income, western settings during the same period. While 42 patients (63.9%) received some form of surgical treatment, only 21 patients (29.2%) received adjuvant treatment. More striking is that only 6 of the 21 patients received their adjuvant treatment at the study center while the other 15 patients had to go abroad to receive their adjuvant treatment. Due to the centralized nature of

Table 1. Descriptive Ethiopian Breast Cancer Statistics from Gebremedhin and Shamebo (1998)

Variable	Mean ± SD or N (%)
Gender	
Female	62 (86.1%)
Male	10 (13.9%)
Female : Male ratio	6.2 : 1
Age (years)	
Females	41.8 ± 12.8
Males	52.1 ± 12.2
Delay in Presentation – median (months)	12
Range	2 - 108
Presenting Symptom	
Breast lump	66 (91.7%)
Ulceration and retraction	29 (40.3%)
Nipple Discharge	13 (18.1%)
Symptoms unrelated to breast	5 (6.9%)
Shortness of breath	3 (4.2%)
Back pain and lower extremity weakness	2 (2.8%)
Tumor Size – mean (cm)	6.5
Range	1.5 – 14
Stage at Diagnosis	
Stage 0	0 (0%)
Stage I	0 (0%)
Stage II	17 (23.6%)
Stage III	29 (40.3%)
Stage IV	26 (36.1%)
Histologic Diagnosis	
Infiltrating ductal carcinoma	53 (73.6%)
Infiltrating lobular carcinoma	7 (9.7%)
Colloid (infiltrating)	2 (2.8)
FNA cytologic diagnosis only	10 (13.9)
Treatment	
Lumpectomy	2 (2.8%)
RM	21 (29.2%)
RM + oophorectomy	2 (2.8%)
RM ± CTx ± RTx ± Tam	21 (29.2%)
Palliative CTx ± RTx ± Tam	33 (45.8%)
Palliative RTx only	3 (4.2%)
Palliative Tam only	4 (5.6%)
Received no treatment	11 (15.3%)

*Abbreviations: RM – radical mastectomy; CTx – chemotherapy; RTx – radiotherapy; Tam - Tamoxifen

cancer care in Ethiopia, chemotherapy and radiotherapy were only available at this one center, Tikur Anbessa Hospital, at the time of the study and, therefore, it seems that over a six year period only six patients in the entire country received both surgery and adjuvant chemo- or radio-therapy treatment for breast cancer domestically. Detailed long-term follow-up is difficult to decipher from this publication.

However, after a median follow-up of 36 months (range 2 - 120 months), 29 patients (40.3%) were still alive, 24 patients (33.3%) deceased, and 19 patients (26.4%) lost to follow-up, though the authors suggested that all the patients lost to follow-up were likely deceased. The study does not give a breakdown of survival by stage at presentation. The authors concluded their discussion with a description of the Ethiopian context for breast cancer care in 1998: “Chemotherapeutic agents are not available in our hospital on a regular basis. As a result, only some rich or desperate patients could import them from abroad and be able to complete [adjuvant] treatment. It is high time that the one tertiary-care center we have in this country be equipped with the means to treat patients with cancer in general and breast cancer in particular” (Gebremedhin & Shamebo, 1998).

While the above studies highlight the high relative frequency of breast cancer diagnoses in Ethiopia, none of them give a reliable clue of what the incidence or mortality rates of breast cancer might be nationwide as these statistics must be calculated from population-based cancer registry data. These retrospective reviews of pathologic cancer diagnoses from selected institutions are well-known to be biased by a number of factors, particularly by the accessibility of tumors and their ability to be biopsied. More accessible tumors (e.g., skin cancers) are diagnosed more frequently than less accessible tumors (e.g., colon cancers). For example, many of the above studies mention a very high prevalence of hepatoma and liver cancers in Ethiopia, but state that most of them are never biopsied due to the risk of bleeding after biopsy and the near impossibility of complex liver resections in the Ethiopian surgical context. Therefore, these studies of relative frequency are helpful in the absence of other studies on Ethiopian breast cancer, but must be considered inadequate for demonstrating the burden of breast cancer or the importance of addressing this disease in the overall health system.

The very first population-based cancer registry in Ethiopia, the Addis Ababa Population-Based Cancer Registry (AAPBCR), was recently established in late 2011. In collaboration with IARC and the African Cancer Registry Network (AFCRN), and with the financial support of the Federal German Ministry of Research and Education, there is now an attempt to register cancer cases in residents of the capital city who are diagnosed either at the central referral hospital, Tikur Anbessa Hospital, or one of 17 other health centers and hospitals. The catchment population of Addis Ababa is estimated to be 3.05 million. To date, there have been no formal publications including data from this registry; however, very brief summary statistics were recently added to the AFCRN website. From January to December of 2012, 2907 cancer cases were registered in this new registry; 912 (31.4%) diagnosed in males and 1995 (68.6%) in females. In women, the three most common cancers were breast cancer (34.0%), cervical cancer (15.8%), and ovarian cancer (6%). Incidence and mortality rates appear to be forthcoming at this time. Figure 1 shows the ten most commonly diagnosed cancers in men and women of the AAPBCR (D. M. Parkin, 2013).

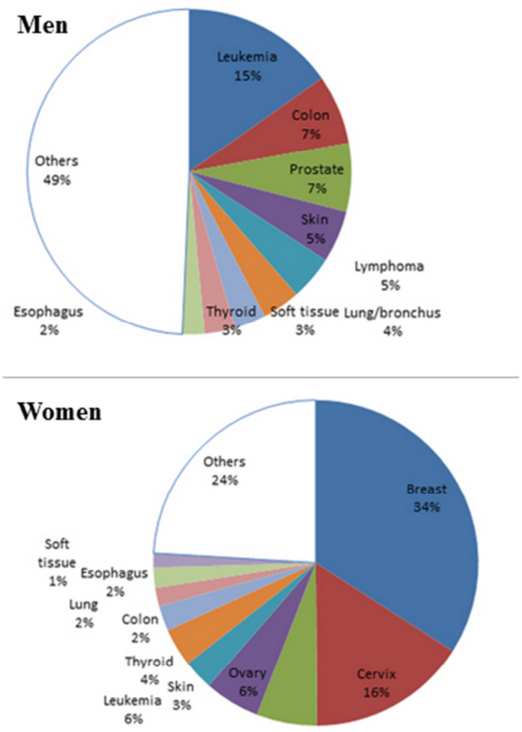

Figure 1. Top 10 Cancer Diagnoses among Men and Women in Addis Ababa, Ethiopia (2012). Reprinted from African Cancer Registry Network, 2013, Retrieved July 27, 2013 from http://afcrn.org/membership/members/100-Addisababa. Copyright 2013 by African Cancer Registry Network.

Cancer Incidence in Five Continents (*CI5*), a publication from the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC), is published every five years with incidence rates from populations all over the world. *CI5* utilizes rigorous techniques to ensure the quality and completeness of the data that is included and is, therefore, widely considered to be the gold standard for global cancer epidemiology and incidence statistics. *CI5* has served as the basis for the GLOBOCAN project and numerous other important studies in cancer epidemiology. In the latest edition (*CI5* vol. IX), published in 2008, cancer incidence in Africa was presented from a mere 5 cancer registries that met criteria for data quality, only two of which were located in sub-Saharan Africa. These registries are located in Sétif, Algeria; Gharbiah, Egypt; Harare, Zimbabwe; Kyadondo County, Uganda; and the Central Region of Tunisia. All of these countries' data, with the exception of Egypt's, were published with a note that care should be taken in interpretation due to its marginal quality and comparability with other countries around the world. Zimbabwe's registry actually had the lowest rate of histologic verification of any country included in CI5.

Despite these shortcomings in quality in the two sub-Saharan cancer registries, the data produced by CI5 still provide a far better idea of cancer incidence in a sub-Saharan LMIC than the studies of relative prevalence that have been performed in Ethiopia. In Uganda, the cancer registry was established in 1954 and has essentially collected cancer data since that time. (There was a period of approximately18 years, from 1971-1989, when data collection was not possible due to the political instability surrounding the coup d'état of General Amin Dada.) The most recent update released from this registry shows increasing incidence rates of cancer in both males and females over the period of 1991 to 2006. Among females, the cancer with the greatest incidence was cervical cancer (ASR 52.4 per 100,000) followed by breast cancer (ASR 31.0 per 100,000) and Kaposi sarcoma (ASR 20.1 per 100,000). While the incidence rate of breast cancer in Uganda remains relatively low compared with the rest of the world, it has shown a marked increase of 4.5% annually. This growth in incidence was most notable in the growing population of postmenopausal women (D. M. Parkin, Nambooze, Wabwire-Mangen, & Wabinga, 2010; H. R. Wabinga, Parkin, Wabwire-Mangen, & Nambooze, 2000). A further publication from this Ugandan registry outlined the age-standardized relative survival (ASRS) for 15 cancer sites or types. The cancers that ranked highest in 5-year ASRS among women were breast (42%), non-Hodgkin lymphoma (26%), and Kaposi sarcoma (21%) (H. Wabinga, Parkin, Nambooze, & Amero, 2011).

The cancer registry in Zimbabwe was established in 1985 in collaboration with IARC and reached adequate population coverage to produce incidence estimates in 1990. Over a 20 year period of registration (1991-2010) the overall risk of cancer increased in both sexes and the most common cancers diagnosed among women were cervical (24.6%), Kaposi sarcoma (17.4%), and breast cancer (10.4%). By 2010 the age-standardized incidence rate of breast cancer had increased to 47.8 per 100,000 with statistically significant growth of 4.9% annually. Again, this growth in breast cancer incidence was most evident in older women (after age 50). Based on trends of all the cancers studied, the authors note that there is an emerging burden of cancers associated with a "westernized" lifestyle (e.g., breast, prostate, lung, and large bowel) while the burden of those traditionally associated with poverty and infection (e.g., cervix, liver, and esophagus) have shown little to no decline in incidence (Chokunonga, Borok, Chirenje, Nyakabau, & Parkin, 2013; Chokunonga et al., 2000). Regarding survival, ASRS rates were recently reported for 17 tumor sites or types of cancer. Among women, the highest 5-year ASRS rates were seen for melanoma (83%), cancers of the eye (74%), and breast cancer (62%) and marked disparity was noted in the survival of white and black Zimbabweans (Chokunonga, Borok, Chirenje, Nyabakau, & Parkin, 2011).

These data from Zimbabwe and Uganda are the only incidence and survival statistics that have been directly recorded in sub-Saharan Africa in a reliable and high-fidelity manner. They are the result of population-based cancer registration, which will be discussed in the coming section.

CANCER REGISTRATION

A cancer registry is a compilation, either paper or electronic, of all cancer cases that have been diagnosed in a defined population. These registries record demographic particulars of patients and the clinical and pathological characteristics of their cancers. After continuous and systematic enrollment of patients in a registry, the data are then able to be analyzed and interpreted on a periodic basis to provide information about any given cancer in the population and the characteristics of those patients who were diagnosed with it, or cancer trends overall. These periodic analyses and the descriptive statistics produced allow for: (a) temporal, geographic, and other trends in incidence to be observed; (b) the generation of hypotheses that might explain the observed differences through further epidemiologic study;

and (c) planning and evaluation of the national health system in which the registry is based with regards to prevention, diagnosis, and treatment of cancer (Jensen et al., 1991; D. M. Parkin, Ferlay, et al., 2010).

In establishing a program of cancer epidemiology, two broad categories of cancer registry can be established, a hospital-based cancer registry or a population-based cancer registry. Hospital-based cancer registries record all patients who are diagnosed with cancer in a given institution, including general information about treatment they receive and the outcome. This type of registry is very useful for administrative purposes within the hospital, such as monitoring the treatment cancer patients receive and improving the quality of their care. The limitation of hospital-based registries, however, is that a catchment population, or area, is not able to be defined and therefore an incidence of cancer is not able to be calculated. Population-based cancer registries are explicitly established within a known catchment population because the goal is to capture and register every new case of cancer that occurs in that discrete population. While some population-based cancer registries are able to cover an entire country's population, more often they cover smaller, subnational areas. This is particularly true in developing countries where a registry may only cover a major city, often the capital city. Regardless of the size of the catchment population, the focus of these population-based registries is epidemiology and public health and from their data, incidence and a host of other valuable statistics are able to be measured (Dos Santos Silva & International Agency for Research on Cancer., 1999; Ferlay et al., 2010a).

Cancer registration had its inauspicious early stages in 1728 in London when an unsuccessful attempt at a cancer census is thought to have been first attempted. This effort was followed by numerous unsuccessful attempts at "mandatory" censuses that were met with little enthusiasm or response from the physicians surveyed for nearly 300 years. The first successful attempts at cancer registration occurred in the early 20th century after cancer was made a notifiable disease in England, Germany, and the United States with the hope of furthering etiologic research. Methodologically, individuals diagnosed with cancer were continuously recorded on paper cards by diagnosing physicians and sent to central card indices maintained by a registry staff that eliminated duplicate cases and attempted to complete missing reports. The Hamburg Cancer Registry in Germany is considered to be the oldest example of a modern cancer registry. In 1929, it was the first registry to establish an official status with the regional Public Health Department and to secure funding for a staff of nurses to visit hospitals and medical practitioners in the region at regular intervals for data collection and follow-up. The Connecticut Tumor Registry, fully established in 1941, is considered to be the first population-based cancer registry with epidemiological and ecological objectives. After this time a number of other population-based cancer registries began to be established in the United States and Canada. The biggest impetus for cancer registry establishment is thought to have come from the official recommendation of Dr. Clemmesen, the Director of the Danish Cancer Registry, and 12 internationally recognized cancer experts, to a commission of the WHO in Copenhagen in 1946. Their recommendation for worldwide establishment of cancer registries suggested that (Jensen et al., 1991):

1. "great benefit would follow the collection of data about cancer patients from as many different countries as possible;
2. "such data should be recorded on an agreed plan so as to be comparable;
3. "each nation should have a central registry to arrange for the recording and collection of such data;
4. "there should be an international body whose duty it should be to correlate the data and statistics obtained in each country" (p. 5).

Four years later, in 1950, the WHO established a formal subcommittee that focused on making cancer registries a priority and in 1965 the International Agency for Research on Cancer (IARC) was established as a specialized cancer research center of the WHO. Since then, many population-based cancer registries have been established around the world such that there are now more than 400 populations with a cancer registry (Dos Santos Silva & International Agency for Research on Cancer., 1999; Jensen et al., 1991). These registries, however, are largely concentrated in high-income, developed countries where the resources required to establish programs of cancer epidemiology are more readily available. As mentioned above, IARC reliably evaluates the data quality and completeness for all registries that submit data for publication in *Cancer Incidence in Five Continents* (*CI5*). Registries with poor quality data, incomplete population coverage, a low proportion of histologically verified cases, or a high proportion of so-called “death certificate only” (DCO) cases are not included in the publication. In the most recent edition of *CI5*, Volume IX, data was accepted from 300 populations, 225 cancer registries, and 60 countries, with 106 populations being rejected due to poor data quality. IARC estimates that 11% of the world’s population is represented in this compilation of cancer data and Table 2 above shows the geographic coverage by country, registry, and population group. The population coverage by region includes 258.5 million from North America (80%), 238.8 million from Europe (33%), 152.3 million from Asia (4%), 23 million from Oceania (73%), 23 million from South and Central America (4%), and 8.8 million from Africa (1%). ("Cancer incidence in five continents. Volume IX," 2008) This coverage of less than 1% of the African population further demonstrates the tremendous paucity of quality epidemiology currently being done in African countries like Ethiopia. A recent literature review of all cancer registration articles published between 2006 -2008 found that while breast cancer was the most common specific cancer covered in registries, less than 1% of these studies were performed in Africa (APOCPC/UICC-ARO Cancer Registration Consortium, 2008).

Table 2. Geographical Coverage by country, registry, and population group from *CI5* vol. IX(2008)

	Countries		Registries		Populations	
	Submitted	Accepted	Submitted	Accepted	Submitted	Accepted
Africa	14	5	16	5	16	5
South and Central America	11	8	29	11	29	11
North America	2	2	58	54	136	118
Asia	18	15	77	44	84	50
Europe	30	29	120	100	123	100
Oceania	6	4	13	11	18	16
Total	80	60	313	225	406	300

Note: The sum of the individual countries is greater than the total, reflecting the fact that some countries are present in more than one continent

While cancer registration and epidemiology continue to be rare in sub-Saharan African, the need to establish cancer registries has been prioritized as an essential step forward in improving or, in many cases, developing *de novo* national cancer control programs. (Anderson et al., 2011; APOCPC/UICC-ARO Cancer Registration Consortium, 2008; Dos Santos Silva & International Agency for Research on

Cancer., 1999; D. Maxwell Parkin et al., 2003; South Africa National Cancer Registry., 1995; Valsecchi & Steliarova-Foucher, 2008; World Health Organization & International Agency for Research on Cancer, 2013a) LMICs are a heterogeneous group with obvious challenges in their economies and the health systems that vary by country. Suboptimal cancer care, however, is one thing that many of these LMICs have been demonstrated to have in common due to a foregoing focus disproportionately on the burden of communicable disease in the formulation of their health systems. The Breast Health Global Initiative (BHGI) is a group that is recognized for leading an international movement to improve breast cancer care in LMICs and striving to "develop, implement, and study evidence-based, economically feasible, and culturally appropriate" guidelines for this context. The most recent summit of the BHGI in 2010 updated their comprehensive set of recommendations for LMICs and these recommendations clearly underscore the primary importance of understanding the burden of breast cancer in a given country and establishing population-based cancer registries where they do not exist. (Anderson et al., 2011; Breast Health Global Initiative, 2013) The Global Initiative for Cancer Registry Development in Low- and Middle-Income Countries (GICR), a special committee convened by IARC, WHO, and several other major regional, national, and international cancer organizations, was recently launched in 2011 with the goal of placing cancer surveillance on the emerging global noncommunicable disease agenda. Through collaborations with IARC several population-based registries have already been successful established in LMICs (e.g., Zimbabwe, Uganda) and through the continued efforts of GICR, IARC is focusing its efforts in the Middle East, North and sub-Saharan Africa, Asia and Central and South America to continue the establishment of new registration sites. In each instance, their stated goal is "to produce reliable, high-quality information on the burden of cancer so that effective policies for cancer control may be developed, implemented and evaluated" (World Health Organization & International Agency for Research on Cancer, 2013a).

In 2012, GICR established a formal relationship with the African Cancer Registry Network (AFCRN), which is an organization originally started in 2011 as the East African Cancer Registry

Network through funding from the Doris Duke Charitable Foundation and now receiving ongoing financial support from the International Network for Cancer Treatment and Research (INCTR). As indicated by the name, AFCRN works around Africa to improve the effectiveness of cancer surveillance programs and they have become the regional hub for GICR's activities in Africa. The AFCRN, despite a paucity of published data, states there are network-member population-based registries now functioning and collecting data in 18 African countries: the Democratic Republic of Congo, Cote d'Ivoire, the Gambia, Ghana, Guinea, Kenya, Malawi, Mauritius, Mozambique, Niger, Nigeria, Rwanda, the Seychelles, South Africa, Tanzania, Uganda, Zimbabwe, and, now, Ethiopia, after the recently established population-based cancer registry in Addis Ababa.

BREAST CANCER STAGING AND OUTCOMES

A fundamental basis on which cancer registration rests is cancer staging. When a patient is diagnosed with cancer, the staging process determines where the cancer started and how much it has spread. The original tumor is called the primary tumor and, in the case of malignant, or cancerous, tumors, they are able to spread to regional lymph nodes or distant locations or organs. Cancer staging uses a precise, standardized language to describe how advanced the primary tumor is and how far it has spread from its initial location. The end result of cancer staging is that each patient is assigned to a category based upon the extent of his/her cancer. There are several methods, or languages, that can be used to stage cancer, the most commonly used being the Tumor-Node-Metastasis (TNM) Staging System of the American Joint Committee on Cancer (AJCC) (Edge et al., 2010). This staging system describes how far the cancer has spread from its point of origin by direct extension (Tumor Stage), through the lymphatic system (Lymph Node Stage), and to distant sites (Metastasis

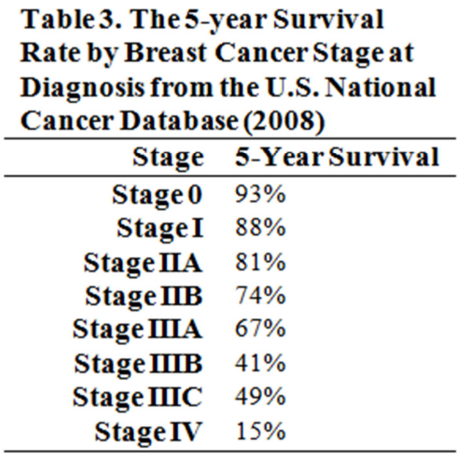

Table 3. The 5-year Survival Rate by Breast Cancer Stage at Diagnosis from the U.S. National Cancer Database (2008)

Stage	5-Year Survival
Stage 0	93%
Stage I	88%
Stage IIA	81%
Stage IIB	74%
Stage IIIA	67%
Stage IIIB	41%
Stage IIIC	49%
Stage IV	15%

Stage). In breast cancer, the *tumor stage* classifies the primary tumor based on its size and direct extension, or growth, into adjacent tissues. Increasing numeric values (ie. T1, T2, T3, T4) correlate with increasing size and/or increasing directextension of the tumor. Breast cancer most commonly metastasizes, or spreads, via the flow of lymphatic vessels and checking lymph nodes for metastasizing cancer is also of critical importance. The *lymph node stage* similarly classifies the extent to which cancer has spread to the lymph nodes in the area of the breast with increasing nodal stage (ie. N1, N2, N3) signifying increasing lymph node involvement. Thirdly, the *metastasis stage* essentially records whether the primary tumor has spread to any distant location or organ in the body. Metastases are either present (M1) or absent (M0). Each of these individual three stages are then combined as components of an overall summary stage ranging from Stage 0 pre-invasive, pre-cancer to Stage IV metastatic cancer.

In addition to creating a common language that can be used to communicate precise information between healthcare providers, cancer staging provides an important predictor of prognosis, or what will happen in the future, and allows physicians to plan a course of treatment. Patients grouped into the same stage will require similar treatment and have a similar likelihood of survival. Table 3 clearly demonstrates the principle that cancer-related survival is much better when cancer is diagnosed in the earlier, less-advanced stages.

ETHIOPIAN CONTEXT

The context in which breast cancer must be diagnosed and treated in Ethiopia is quite different from what is found in more resourced, Western countries. The barriers which prevent women and men from reaching care in a timely manner, and thus presenting with very late stage cancers, are best described as an amalgam of health system, social, and economic factors.

Breast cancer treatment, in nearly all cases, ought to involve some form of surgical procedure to remove the cancer. The very first surgical education and general surgery residency training to ever take place in Ethiopia began at Addis Ababa University and Tikur Anbessa Hospital in 1980. Since then, the

College of Surgeons of East, Central and Southern Africa (COSECSA), the governing body that oversees surgical education in East, Central and Southern Africa, has recorded the training of only 372 surgeons. While there a number of expatriate surgeons who have additionally come to live and practice in Ethiopia, the net result of tremendous physician migration out of the country has resulted in a surgical workforce estimated to have less than 300 surgeons in a country of somewhere near 90 million inhabitants. In Ethiopia, this results in a surgeon-to-population ratio of approximately 1 surgeon for every 300,000 people, while in the United States there is approximately one surgeon for every 10,523 people (American College of Surgeons Health Policy Research Institute & Association of American Medical Colleges, 2012; Kakande, Mkandawire, & Thompson, 2011). Furthermore, surgeons in Ethiopia are concentrated in Addis Ababa, or one of several other large cities, which further exacerbates the surgeon-to-population ratios in rural areas where surgeons are scarce. The end result is extraordinarily limited surgical capacity in a largely rural Ethiopian population that is required to travel for hours to days to reach surgical care.

Adjuvant treatment for breast cancer includes all nonsurgical treatments like chemotherapy, radiation therapy, and hormone, or endocrine, therapy. Up until approximately 12 months ago, chemotherapy and radiation therapy were only available at the Tikur Anbessa Hospital due to the fact that there are only four oncologists in the country. Chemotherapy has now expanded to being available in three other referral hospitals in the country. The national formulary of drugs and medications that are allowed into the country includes a fairly comprehensive list of oncologic medications; however, in practice, only a small proportion of these medications are actually imported into the country and available. (Ethiopia Ministry of Health, 2008) Regarding radiation therapy, which is critically important in breast cancer treatment, there continues to be a single radiotherapy unit at Tikur Anbessa Hospital with two antiquated, frequently nonfunctional, cobalt-based radiation units serving the second most populous country in Africa. (Reeler, Sikora, & Solomon, 2008)

Pathology is another challenging facet of cancer care in Ethiopia. Pathology serves as the foundation for oncology care since pathologic documentation of malignancy has been the gold standard for decades. Twenty years ago Ethiopia had only four pathology centers where cytology and biopsy specimens could be sent for analysis (Loutfi & Pickering, 1992). The situation has improved somewhat with a greater (unknown) number of pathology centers, most of which function as private pathology laboratories and very few hospitals have their own on-site pathology services. Estrogen and progesterone receptor status, tumor characteristics essential to breast cancer therapeutic evaluation, was first introduced in 2005 in Ethiopia through the Ethiopia Breast Cancer Project of Axios International, a private healthcare consulting firm that received approximately $1.7 million in funding from the pharmaceutical company AstraZeneca to carry out the project. The project also brought hormone therapy into the country for the first time, with two AstraZeneca drugs, tamoxifen and anastrazole, donated at no cost to patients (Dye et al., 2010; Reeler et al., 2008). The project ended after several years and the antibodies needed to test for estrogen and progesterone receptor status are now no longer available in the country due to lack of funding. Hormone therapy with tamoxifen continues to be available, though its efficacy is diminished without knowing the hormone receptor status of patients' tumors.

Several secondary studies funded through the Axios International/AstraZeneca Ethiopia Breast Cancer Project have recently been published that investigate the societal and cultural beliefs that affected breast cancer patients' pursuit of care. De Ver Dye and colleagues, using a mixed quantitative and qualitative methodology, found that:

a) Nearly half of study participants (47%) suggested that women in Ethiopia typically have never heard of breast cancer and know nothing about the disease.

b) Regarding etiology, 55% of participants thought breast cancer is caused by an 'ethnomedical' cause such as difficulties breast feeding or abnormalities caused by exposure to cold, sunlight, heat, or bad air. A smaller proportion (27%) cited biomedical causes such as heredity, diet, and environmental exposures. Some also supported the concept of transmissibility or contagion as a mechanism of acquiring the disease.

c) Approximately 40% of participants indicated a general sense of fatalism in regard to their breast cancer diagnosis, not knowing that treatment was either available or effective.

d) In many cases this fatalism was responsible for patients ignoring symptoms of their cancer and delaying the pursuit of care.

e) There is a common societal belief that treatment for cancer in general cannot be effective and people diagnosed with cancer are without hope. This fatalism caused some to avoid health facilities and hospitals due to their perception that the disease is not treatable.

f) Only 10% of study participants mentioned that some form of stigmatization was a major problem for patients with breast cancer in Ethiopia.

g) Traditional healers were used by more than half of the participants at some point during their experience with breast cancer, as shown in Table 4. The largest proportion (24.6%) sought out a traditional healer before seeking medical care at a hospital or clinic (De Ver Dye et al., 2011).

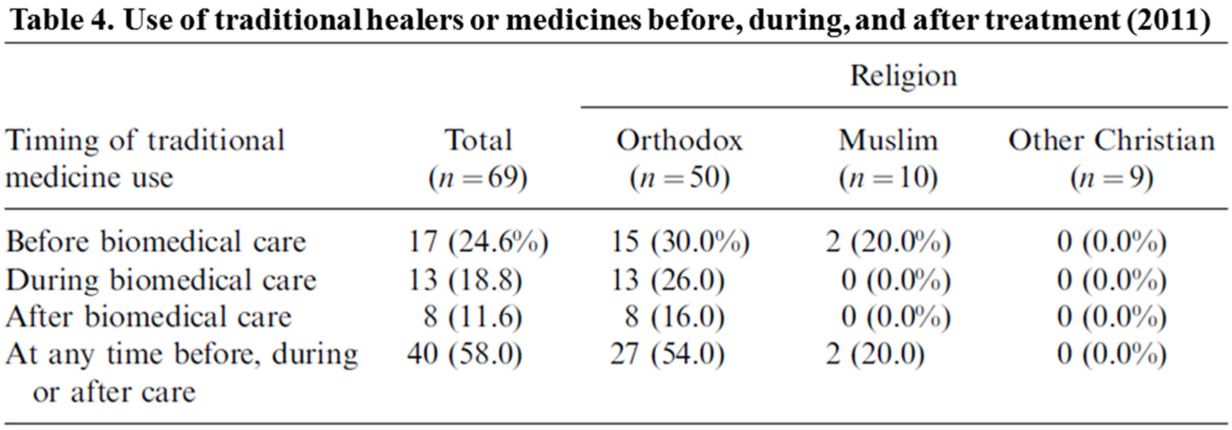

Table 4. Use of traditional healers or medicines before, during, and after treatment (2011)

		Religion		
Timing of traditional medicine use	Total (*n* = 69)	Orthodox (*n* = 50)	Muslim (*n* = 10)	Other Christian (*n* = 9)
Before biomedical care	17 (24.6%)	15 (30.0%)	2 (20.0%)	0 (0.0%)
During biomedical care	13 (18.8)	13 (26.0)	0 (0.0%)	0 (0.0%)
After biomedical care	8 (11.6)	8 (16.0)	0 (0.0%)	0 (0.0%)
At any time before, during or after care	40 (58.0)	27 (54.0)	2 (20.0)	0 (0.0%)

The breast cancer study by Gebremedhin and Shamebo, discussed previously, also included a short discussion of barriers that hamper early detection of breast cancers in Ethiopia. The authors postulate that the foremost barriers are difficult access to modern medical care and the frequent utilization of traditional healers and medicines. Once patients reach medical care at a clinic or hospital, cancer care is still often limited by exceedingly constrained resources and an overloaded, poorly functioning health system. Also suggested from the data in their study is the possibility that women may fear mastectomy. From the cohort of 72, 18 females (25%) refused mastectomy and 24 patients (33%) chose to pursue care from traditional healers after being diagnosed (Gebremedhin & Shamebo, 1998).

Amid a growing burden of breast cancer and other cancers, several cancer-related nongovernmental organizations (NGOs) in Ethiopia have been formed and are ardently working to improve the situation for those with cancer by promoting cancer awareness, encouraging cancer registration, and working to increase the Ministry of Health's commitment to improve cancer prevention and treatment in the country. Some of the most prominent organizations include the Ethiopian Cancer Association (ECA; http://www.yeeca.org/), the Mathiwos Wondu Ethiopian Cancer Society (MWECS; http://www.mathycancersoc.org/), Battling Cancer in Ethiopia (BCE; http://www.bcethiopia.org/), and Cancer Care Ethiopia (CCE; http://www.english.cancercare.no/). All of these NGOs have been formed within the past 10 years, yet in this short history significant collaboration has been developed and leaders of these NGOs have secured prominent roles on Ministry of Health committees responsible for formulating a plan to address the burgeoning burden of cancer and other noncommunicable disease.

CHAPTER 3: METHODS

This research project was supported by a Global Health Research Fellowship provided by the Fogarty International Center of the National Institutes of Health (NIH Research Training Grant R25 TW009337). The research grant provided salary support, travel expenses, and a modest research budget to be used during the ten month period of on-site mentored research lasting from June 2012 to May 2013.

REGISTRATION SITE SELECTION

Ethiopia is notably one of two African countries that were never colonized during imperialization and is the origin of Arabica coffee as well as the Blue Nile River, which is the chief headstream of the Nile River coming from Lake Tana in the northwestern part of the country. Located in eastern Africa on the horn of the continent, Ethiopia is a large country covering 1,104,300 km^2 (10th largest in Africa; 27th largest country in the world) and is bordered by Somalia, Djibouti, Eritrea, Sudan, South Sudan, and Kenya. The country has an overall rugged terrain with a central mountain range that is divided by the northern extension of the Great Rift Valley. Organizationally, the country is divided into 11 regions, nine ethnically-based states and two self-governing city administrations (Addis Ababa and Dire Dawa). (See Figures 1–5 in the Appendix for Ethiopian and Table 5 below which includes the names and populations of each geographic region). Similar to the United States' organization into states, counties, and districts, the regions in Ethiopia are subdivided into zones, zones subdivided into

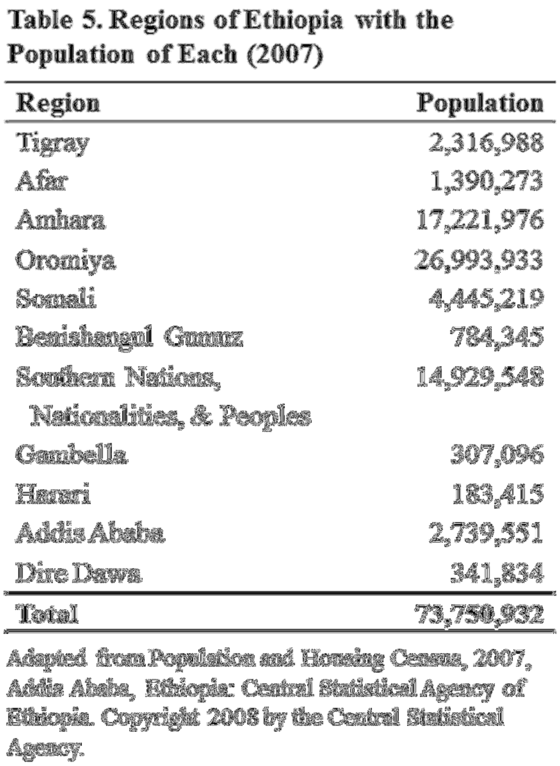

Table 5. Regions of Ethiopia with the Population of Each (2007)

Region	Population
Tigray	2,316,988
Afar	1,390,273
Amhara	17,221,976
Oromiya	26,993,933
Somali	4,445,219
Benishangul Gumuz	784,345
Southern Nations, Nationalities, & Peoples	14,929,548
Gambella	307,096
Harari	183,415
Addis Ababa	2,739,551
Dire Dawa	341,834
Total	73,750,932

Adapted from Population and Housing Census, 2007, Addis Ababa, Ethiopia: Central Statistical Agency of Ethiopia. Copyright 2008 by the Central Statistical Agency.

woredas, and woredas subdivided into kebeles (Ethiopia Central Statistical Agency, 2007; United States Central Intelligence Agency, 2012).

The population of Ethiopia is currently estimated to be 93.9 million (2nd most populous in Africa; 13th most populous in the world), though estimates vary significantly with some estimates as low as 80 million. The population is largely rural (83%) and quite diverse, with nearly 90 different languages spoken by as many or more ethnic groups. Ethiopian Orthodox is the predominant religion (43.5%) followed by Muslim (33.9%), Protestant (18.6%), traditional beliefs & animism (2.6%), Catholic (0.7%), and other (0.7%). The population pyramid of Ethiopia is broad-based, similar to that of many low-income countries, and the life expectancy for males is estimated to be 58 years and for females is 62 years (United States Central Intelligence Agency, 2012).

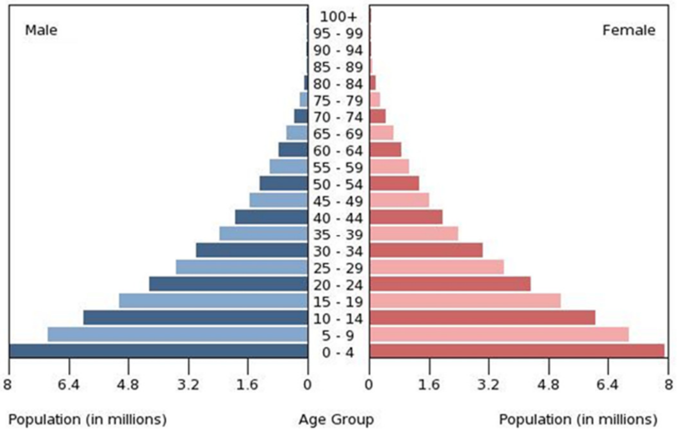

Figure 2. Ethiopia Population Pyramid (2013). Reprinted from CIA Factbook: Ethiopia, 2013, Retrieved from https://www.cia.gov/library/publications/the-world-factbook/geos/et.html. Copyright 2013 by the United States Central Intelligence Agency.

The selection of sites, or hospitals, in which to establish cancer registries was heavily influenced by a longstanding collaboration between the health sector of Ethiopia and Emory University and more recently the Global Surgery Program (GSP) of the Department of Surgery in the Emory University School of Medicine. Dr. Jonathan Pollock, an Assistant Professor in the Department of Surgery and Founding Director of the GSP, lives in Ethiopia year-round where he practices surgery and trains surgical residents in the Pan-African Academy of Christian Surgeons (PAACS) surgical residency. The PAACS training program is primarily based in two private hospitals in Ethiopia: Myungsung Christian Medical Center (MCM) in the capital city, Addis Ababa, and Soddo Christian Hospital (SCH) in the rural southern town of Wolayita Soddo. To improve the sustainability and permanence of these cancer registries, we chose to initially work in these two hospitals (MCM and SCH) where Dr. Pollock, a contributor to this research, would be able to facilitate their establishment and maintenance.

Subsequently, supplementary research funding allowed us to expand registration efforts to two further hospitals. Discussions with the oncologists at Tikur Anbessa Hospital alerted us to their nascent effort to establish a population-based cancer registry in the capital city. Desiring not to compete with their efforts, but rather to complement them, we chose to expand our efforts to two other hospitals in the rural Wolayita zone, which is the same zone in which SCH is located. (Surgical services in Ethiopia are designed to be available at the level of the zonal, or district, hospital, as specified by the Ministry of Health. Patients with breast cancers diagnosed at small clinics or lower levels of care, therefore, ought to be referred to the zonal hospitals for surgical consultation and treatment.) In Wolayita three hospitals serve the zonal population, SCH and two others. (In the Appendix, Figure 5 shows the location of the two towns, Soddo and Areka, in which these three hospitals are located). We therefore chose to establish cancer registries in the other two Wolayita hospitals, a private hospital, Dubbo St. Mary Catholic Hospital, and the government hospital, Otona Wolayita Soddo Hospital. While establishing registries in these three hospitals is not sufficient for zonal population coverage (ie. for a population-based cancer registry), we desired to concentrate our efforts in this geographic region such that further case finding in small and medium clinics could later be added to improve coverage. Below is a brief overview of each of the four hospitals in which we established cancer registries:

1. ***Myungsung Christian Medical Center*** (MCM), located in the capital city Addis Ababa, is a private, non-profit referral hospital opened in 2004 under the leadership of physicians and others from Myungsung Presbyterian Church in Seoul, South Korea. Due to a continuing relationship between Korea and Ethiopia stemming from the Korean War era, the Prime Minister of Ethiopia requested the construction of this hospital of the Korean government in 1993. Since its opening, the hospital has earned a reputation of having some of the best quality medical care in the country, including medical, surgical, radiologic, obstetrics, subspecialty, and laboratory services

in a modern medical complex. MCM also completed the construction of a new medical college approximately 12 months ago and admitted their first class of medical students.

2. ***Soddo Christian Hospital*** (SCH), located in the rural southern town of Wolayita, Soddo, is approximately 330 km southwest of Addis Ababa and opened in January 2005 as a private hospital under the ownership of the non-profit St. Luke's Health Care Foundation (Wheaton, IL). The hospital is accredited by the Ministry of Health for 199 beds and currently the hospital compound has 22 major buildings. SCH is a major referral center for the surrounding rural region with medical, surgical, subspecialty, laboratory, and pathology services. It functions as an academic medical center with specialty residency training in surgery and orthopedic surgery, master training in Emergency and Essential Surgery, and an active program of clinical research. SCH has signed a Memorandum of Understanding (MOU) with the recently opened Wolayita Soddo University School of Medicine and maintains an active role in training medical students and clinical officers.
3. ***Otona Wolayita Soddo Hospital*** (OWSH), also located in the rural town of Wolayita Soddo, is a government hospital that was initially opened as a mission hospital around 1970. The government took over the hospital when a communist regime (The Dergue) assumed control of Ethiopia in 1974. The hospital has remained under government control since that time and, like other government hospitals in the region, it struggles with very constrained resources and a limited staff. Surgical services have been continuously available at the hospital for only the past 5 years and physicians see a fairly large number of women referred for breast cancer treatment.
4. ***Dubbo St. Mary Catholic Hospital*** (DSM) is a referral hospital located in Bolosso Sore Areka, which is also in the Wolayita zone and approximately 40 km north of Soddo town. The hospital opened as a private hospital in 2002 under the leadership of the Catholic Church and primarily focused on improving the health and nutrition of mothers and children. The hospital has since expanded and is now providing general medical, surgical, gynecologic, and radiology services.

REGISTRY ESTABLISHMENT

In preparation for registry establishment, significant effort was spent learning registry best practices from local cancer registrars and registration experts in the Atlanta, Georgia area. Time was spent observing cancer registrars from hospital-based registries (Emory University Hospital and the Atlanta Veterans Affairs Medical Center) with particular attention paid to patient health information confidentiality, case finding, abstraction practices, and registrar training resources. Time was also spent meeting with the Director of the Georgia Center for Cancer Statistics (Kevin C. Ward, PhD, MPH, CTR) who also serves as the principal investigator for the Surveillance Epidemiology and End Results (SEER) Registry in Georgia. He was able to share previous experiences and insights from establishing a separate cancer registry *de novo* in a foreign country. Invaluable books, manuals, and training guides related to cancer staging and registration were donated to the Ethiopian Breast Cancer Registry.

Case finding and data abstraction began in August 2012. Case finding can rely on a variety of source data to identify diagnosed cases of cancer. In a context where cancer registration has never existed, as it has not here, there is no existing paradigm to support the idea of cancer being a notifiable disease or one for mandatory reporting. The case finding process in each of the hospitals, therefore, was an entirely active process that consisted of looking through registers and logbooks from any clinical department where breast cancer patients would be found. The primary source for case finding in developed countries is usually pathology reports. In Ethiopia, none of the hospitals have internal pathology services and there was not logistical option for cancer reporting or passive case finding that would have resulted in comprehensive case finding. Logbooks or binders recording pathology results were the first sources sought out at each hospital and these were present for review at MCM and SCH. The only record of pathology results at DSM and OWSH were in patients' charts, which first had to be identified from other logs. Other potential sources for data, e.g. formal death certificates, are rarely completed in Ethiopia and varied widely between hospitals. Death certificates seemed to be done primarily for billing reasons and when done, the records were often incomplete. Therefore death certificates were not used as a case finding or data source. Also, in the absence of any screening mammography programs, no radiology reports existed to be scoured for breast cancer cases.

Therefore, in addition to pathology logs, all of the following logbooks or electronic logs were used for case finding at each hospital when available: Operating Room logbook, Minor Procedure logbook, Surgical Outpatient Department logbook, Surgical Admission logbook, and Surgical Referral Clinic logbook. Due to imprecise terminology used in many of these logs (e.g., chief complaint of "breast lump"), a very wide range of terms had to be used in identifying patients in whom breast cancer might have been diagnosed. Many of these cases would be excluded upon chart review after being found to be some other form of non-malignant pathology.

Case finding lists were recorded in a separate case finding logbook which could then be photocopied or given directly to personnel in medical records for the charts to be found. While different record and chart keeping practices were utilized at each hospital, finding the needed charts proved to be a difficult task at each institution. Charts of patients seen within the past year were typically kept in a fairly orderly fashion in a medical records room or office within the hospital. However, due to the amount of space required to store paper charts, charts older than a year were kept in some form of storage room or industrial steel freight container. These storage rooms were often windowless, dark, and completely unorganized (See Figure 3). Finding charts was incredibly laborious and often unsuccessful, resulting in potential breast cancer cases never being identified. Additionally, medical records personnel were often the employees responsible not only for finding the charts of patients

Figure 3. Storage of Medical Records Older than One Year at Otona Wolayita Soddo Hospital (2013). Photo credit: T.P. Love

being seen for follow-up clinical care, but registering all new patients who came to the hospital each day and making each one a new chart. Due to this demanding work load addressed by limited personnel who often lacked insight into the importance of medical research, finding charts for the breast cancer registry was slow and frequently met with significant resistance by the employees in the Medical Records department.

Prior to initiating chart abstraction, a comprehensive breast cancer-specific abstraction form was developed. To ensure comparability of data, variables and data items included in the abstraction form were taken from the Collaborative Staging System of the American Joint Committee on Cancer (AJCC) (Collaborative Staging Task Force of the American Joint Committee on Cancer, 2007). The coding and definitions of the International Classification of Disease for Oncology, Third Edition, (ICD-O-3) were used for topography and morphology. To facilitate accurate, reliable, and standardized data collection, when possible, multiple option response and check boxes were used on the abstraction form rather than free response. The variables abstracted for each patient included demographics (ie. name, age, gender, residence location), date of breast cancer diagnosis (i.e. incidence date), time from onset of breast related symptoms to presentation for care, the source of data abstracted, surgical and adjuvant treatment details, date and status at last contact with patient, and variables essential for staging regarding tumor size, tumor extension, lymph node status, and metastatic status. (See Figure 6 in the Appendix for Ethiopia Breast Cancer Registry Data Abstraction Sheet which includes all variables abstracted for each patient). Pathology services and reports are essential for cancer registration and these were especially difficult to obtain in some institutions. IARC CI5 uses the percent of cases that are verified microscopically (%MV) as one of the main indicators of the validity of information contained in a registry. A %MV that is very high suggests case finding methodology too heavily focused on pathology records while a low %MV suggests inadequate pathologic diagnoses and therefore validity ("Cancer incidence in five continents. Volume IX," 2008). While many breast cancers in this cohort were diagnosed based on clinical evidence or physical examination (i.e. without microscopic tissue confirmation), microscopic verification of diagnoses were meticulously sought out for each patient to avoid erroneous enrollment of other pathologies that might present clinically as locally advanced breast cancer (e.g., sarcoma, breast tuberculosis) (Holcombe, Weedon, & Llwin, 1999). Data abstraction from medical files was performed either by the principal investigator (TPL) or by locally trained cancer registrars. All cases abstracted by registrars were checked for completeness and accuracy by the principal investigator prior to entry into the database.

In order to determine not only breast cancer incidence but also mortality statistics, collection of outcome data also represent a vital part of cancer registries. For many patients, the date of discharge from clinic or inpatient hospitalization at time of diagnosis was their last date of follow-up or contact. Follow-up, therefore, was an active process which was done by contacting all patients with a telephone number listed in their chart. A research assistant fluent in four regional languages called all patients for whom a working telephone number was available to ascertain information regarding further treatment, recurrence, and survival.

All patient data collected for the abstraction form were then entered into an electronic registry. The open source registry software package, CanReg5, developed by and freely available from IARC (Lyon, France), was chosen as the software of choice. While other registry software packages exist, CanReg5 was chosen because it is a free program (i.e. sustainability) and it is being used in nearly all registries established in resource-limited settings. ("Cancer incidence in five continents. Volume IX," 2008) The Ethiopia Breast Cancer Registry (EBCR) was programmed with all necessary variables and dictionaries in CanReg5 to accommodate AJCC and ICD-O-3 standard definitions. EBCR was initially setup on an encrypted, password-protected, and locked research laptop to allow portability between sites. The registry was subsequently installed on two registry desktop computers, one in Addis Ababa at MCM and the other in Wolayita Soddo at SCH, for continued data entry at each site. The data from these two computers are able to be exported and merged with the central registry data present on the laptop.

Analysis for quality control and duplicate cases was performed within CanReg5. Descriptive statistical analysis was then performed using the software package SAS version 9.3 (Cary, NC).

REGISTRAR TRAINING

At each institution one or two nurses from the surgical department were identified as registrar candidates. The concepts of the cancer registration and epidemiology were explained and those interested in participating in this work were recruited for registrar training. A separate project manager was hired from SCH to oversee the activities of registrars at each of the participating institutions and ensure the quality and consistency of their work. The project manager was additionally responsible for electronic data entry of abstraction forms collected from the three hospitals located in the Wolayita Zone (SCH, OWSH, DSM).

The project manager and all registrars attended a one-day-long training seminar taught by the principal investigator. The seminar covered the topics of cancer biology and carcinogenesis, breast anatomy, breast cancer evolution, breast cancer operations and other treatments, and the techniques necessary for cancer staging and registration, including all pertinent AJCC and ICD-O-3 terminology and definitions. Seminar didactics included interactive case discussions drawn from commercially available registrar training materials (Fritz, Currence, Leventhal, Harrison, & Vance, 2011). Print materials and references were distributed to each of the registrars for study and future reference.

Registrar remuneration was determined after significant investigation into local salaries and practices. After weighing the advantages and disadvantages of various compensation systems, a piecework payment model was selected over a salaried position to incentivize productivity and thorough case finding. Negotiations determined that registrars be paid 50 Ethiopian birr (50.00 Ethiopian birr = US $2.67 as of June 28, 2013) per completed abstraction sheet, which was to include all requisite activities of case finding, chart finding, follow-up, and abstraction. Prior to payment, the quality of abstraction was checked for each patient not abstracted by the principal investigator and errors in abstraction were used as opportunities for continuing registrar education.

APPROVALS

A complete description of this proposed research program and methods were submitted to the Emory Institutional Review Board (IRB) for review. The study was deemed to be exempt from review per Emory IRB policies and federal regulations. Despite the international location of this registry, all patient information was maintained with U.S. Health Insurance Portability and Accountability Act (HIPAA) compliant practices. All paper records containing patient information were kept under lock and key in a secure office building environment and electronic data were maintained on password-protected computers that had undergone drive encryption.

Approval to initiate registry activities in each participating hospital was done on a case by case basis after the completion of various applications, letters, and meetings to gain acceptance. This was not a straightforward process and required the navigation of significant bureaucracy, the hiring of additional, unsolicited research staff, and even the teaching of a core medical school course by the principal investigator in order to obtain the proper approvals needed.

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Additional funding was received in the form of a Surgical Oncology research grant in the amount of $20,000 from the Outreach Committee of National Presbyterian Church in Washington, D.C. A donation was given to the church in honor of Mr. Charles Proctor who had lost numerous family members, and subsequently his own life, to cancer and desired to support surgical oncology research in low-resource settings. A request for applications was announced in August 2012. After submitting a formal proposal, we were notified in November 2012 that our research proposal would be funded and that there would be no term for the utilization of funds.

CHAPTER 4: RESULTS

BREAST CANCER DESCRIPTIVE STATISTICS

Over the period of July 2012 to May 2013, 318 breast cancer cases were registered with incidence dates ranging from September 2005 to March 2013. Cases were registered from the four participating hospitals at which cancer registrars had been trained: Myungsung Christian Medical Center (MCMC; 137 cases), Soddo Christian Hospital (SCH; 88 cases), Otona Wolayita Soddo Hospital (OWSH; 44 cases), and Dubbo St. Mary Catholic Hospital (DSM; 49 cases). Table 6 summarizes the results of statistical registry analysis for males, females, and the combined cohort.

Patients were predominantly female (94.3%) with a female to male ratio of 16.7:1. The age of breast cancer patients was quite young with mean and median ages of 41.3 and 40 years respectively. Men diagnosed with breast cancer were, on average, nearly 15 years older than females and no men in this cohort were diagnosed with breast cancer before the age of 30. The variable denoted as "Delay in Presentation" records the period of time from the onset of breast related symptoms, likely noted by the patient directly, to the time of presentation at a health facility for primary diagnosis. Both men and women's presentation was significantly delayed by a median of 12 months, though some individuals reported having breast related symptoms, typically a palpable mass, for as long as 15 years before presentation.

Pathologic diagnosis is difficult to obtain in Ethiopia where there are very few pathologists, particularly in rural areas as most pathologists are concentrated in the capital city. In this cohort, 229 (72%) patients had some form of microscopic verification, either cytologic examination after fine needle aspiration or histologic examination of a core needle biopsy or surgical specimen. The percent microscopically verified (%MV) was slightly higher in women (72.3%) than in men (66.7%) and much higher in the urban MCMC hospital as compared with the other rural hospitals. (See Table 7.) "Clinical diagnosis only" in Table 6 denotes the proportion of patients in whom no microscopic verification was performed and the breast cancer diagnosis was made solely based on clinical examination.

Table 6. Summary Statistics from Ethiopia Breast Cancer Registry

	Male (N=18) Mean ± SD or N (%)	**Female (N=300)** Mean ± SD or N (%)	**Total (N=318)** Mean ± SD or N (%)
Treatment Facility			
Myungsung Christian Medical Center	2 (11.1)	135 (45.0)	137 (43.1)
Soddo Christian Hospital	6 (33.3)	82 (27.3)	88 (27.7)
Otona Wolayita Soddo Hospital	5 (27.8)	39 (13.0)	44 (13.8)
Dubbo St. Mary Catholic Hospital	5 (27.8)	44 (14.7)	49 (15.4)
Age (years)	54.9 ± 14.4	40.5 ± 11.7	41.3 ± 12.3
Median	58	40	40
Range	30 – 78	16 – 80	16 – 80
Age Groups (years)			
Less than 20	0 (0)	3 (1.0)	3 (0.9)
20-29	0 (0)	38 (12.7)	38 (12.0)
30-39	3 (16.7)	107 (35.7)	110 (34.6)
40-49	4 (22.2)	83 (27.7)	87 (27.4)
50-59	3 (16.7)	43 (14.3)	46 (14.5)
60-69	5 (27.8)	18 (6.0)	23 (7.2)
70-79	3 (16.7)	7 (2.3)	10 (3.1)
80 or greater	0 (0)	1 (0.3)	1 (0.3)
Delay in Presentation (months)	29 ± 36.2	14.4 ± 18.1	15.0 ± 12.0
Median	12	12	12
Range	3 – 120	1 – 180	1 -180
Microscopic Verification	12 (66.7)	217 (72.3)	229 (72.0)
Clinical diagnosis only	6 (33.3)	83 (27.7)	89 (28.0)
Morphology			
Infiltrating ductal carcinoma	11 (61.1)	205 (68.3)	216 (67.9)
Lobular carcinoma	0 (0)	7 (2.3)	7 (2.2)
Mucinous adenocarcinoma	0 (0)	5 (1.7)	5 (1.6)
*missing	7 (38.9)	83 (27.7)	90 (28.3)
Histologic Grade			
Well -differentiated	1 (5.6)	11 (3.7)	12 (3.8)
Moderately differentiated	2 (11.1)	45 (15.0)	47 (14.8)
Poorly differentiated	1 (5.6)	41 (13.7)	42 (13.2)
Undifferentiated	0 (0)	1 (0.3)	1 (0.3)
*missing	14 (77.8)	202 (67.3)	216 (67.9)
Tumor Size (mm)	35.6 ± 15.1	54.3 ± 30.0	53.5 ± 29.7
Median	30	50	50
Range	20 – 70	10 – 200	10 – 200
Tumor Stage			
Tis	0 (0)	0 (0)	0 (0)
T1	4 (22.2)	38 (12.7)	42 (13.2)
T2	3 (16.7)	56 (18.7)	59 (18.6)
T3	0 (0)	22 (7.3)	22 (6.9)
T4	11 (61.1)	184 (61.3)	195 (61.3)

Table 6. Summary Statistics from Ethiopia Breast Cancer Registry

	Male (N=18) Mean ± SD or N (%)	Female (N=300) Mean ± SD or N (%)	Total (N=318) Mean ± SD or N (%)
Nodal Stage			
N0	4 (22.2.)	83 (27.7)	87 (27.4)
N1	10 (55.6)	109 (36.3)	119 (37.4)
N2	3 (16.7)	70 (23.3)	73 (2.8)
N3	0 (0)	9 (3.0)	9 (2.8)
Nx	1 (5.6)	29 (9.7)	30 (9.4)
Metastasis Stage			
M0	15 (83.3)	247 (82.3)	262 (82.4)
M1	3 (16.7)	53 (17.7)	56 (17.6)
Stage at Diagnosis			
Stage 0	0 (0)	0 (0)	0(0)
Stage I	0 (0)	17 (5.7)	17 (5.4)
Stage IIA	3 (16.7)	49 (16.3)	52 (16.4)
Stage IIB	3 (16.7)	20 (6.7)	23 (7.2)
Stage IIIA	0 (0)	19 (6.3)	19 (6.0)
Stage IIIB	9 (50.0)	139 (46.3)	148 (46.5)
Stage IIIC	0 (0)	3 (1.0)	3 (0.9)
Stage IV	3 (16.7)	53 (17.7)	56 (17.6)
Surgical Procedures Performed			
No surgical treatment	1 (5.6)	81 (27.0)	82 (25.8)
Incisional biopsy	0 (0)	1 (0.3)	1 (0.3)
Excisional biopsy	2 (11.1)	18 (6.0)	20 (6.3)
Partial mastectomy	0 (0)	12 (4.0)	12 (3.8)
Simple mastectomy	3 (16.7)	42 (14.0)	45 (14.2)
Modified radical mastectomy	11 (61.1)	154 (51.3)	165 (51.9)
Radical Mastectomy	1 (5.6)	4 (1.3)	5 (1.6)
Lymph biopsy or axillary dissection only	1 (5.6)	6 (2.0)	7 (2.2)
Adjuvant Treatment Referral			
Chemotherapy	4 (22.2)	83 (27.7)	87 (27.4)
Radiotherapy (adjuvant or palliative)	3 (16.7)	52 (17.3)	55 (17.3)
Endocrine Therapy Received	0 (0)	32 (10.7)	32 (10.1)
Follow-up (months)	5.4 ± 8.0	8.7 ± 15.3	8.5 ± 15.0
Median	2.0	1.3	1.4
Range	0 – 23.2	0 – 81.3	0 – 81.3
Deaths	1 (5.6)	31 (10.3)	32 (10.1)
Locoregional Recurrence	2 (11.1)	28 (9.3)	30 (9.4)

Infiltrating ductal carcinoma was the predominant morphology (67.9%, or 94.3% of microscopically verified (MV) cases) followed by infiltrating lobular carcinoma (2.2%, or 3.1% of MV) and mucinous carcinoma (1.6%, or 2.2% of MV). Only 32.1% of patients had a histologic grade recorded, moderately differentiated being the most common. This partly demonstrates the poor quality of pathology services in that 55.5% of patients with microscopically verified diagnoses of breast cancer did not have complete analysis of their specimens reported with histologic grade.

Measured as the greatest linear dimension of a tumor, both mean and median tumor sizes, 53.5 mm and 50 mm respectively, indicate very large tumors at presentation. Tumor stage was further worsened by the frequency with which tumor extension progressed to ulceration, *peau d'orange*, or ipsilateral satellite skin nodules by the time of diagnosis, with more than 61% of patients presenting with a T4 lesion. Median nodal stage among patients was N1 and 17.6% of patients presented with evidence of distant metastases at the time of initial diagnosis. Overall stage is as shown in Table 6 with more than 70% of breast cancers being diagnoses at stage IIIA or later and not a single patient being diagnosed with *in situ*, or Stage 0, disease. In Table 7 below, the stage at presentation is further broken down by institution and demonstrates the late stage at presentation regardless of whether the institution is located in an urban (MCMC) or rural (SCH, OWSH, and DSM) area .

Table 7. Microscopic Verification and Stage Analysis by Institution

	MCMC (N=137)	**SCH (N=88)**	**OWSH (N=44)**	**DSM (N=49)**	**Total (N=318)**
Microscopic Verification (%)	137 (100.0)	57 (64.8)	22 (50.0)	13 (26.5)	229 (72.0)
Stage I	10 (7.3)	4 (4.6)	1 (2.3)	2 (4.1)	17 (5.4)
Stage IIA	25 (18.3)	15 (17.1)	2 (4.6)	10 (20.4)	52 (16.4)
Stage IIB	12 (8.8)	4 (4.6)	3 (6.8)	4 (8.2)	23 (7.2)
Stage IIIA	9 (6.6)	5 (5.7)	3 (6.8)	2 (4.1)	19 (6.0)
Stage IIIB	59 (43.1)	39 (44.3)	25 (56.8)	25 (51.0)	148 (46.5)
Stage IIIC	0 (0)	2 (2.3)	0 (0)	1 (2.0)	3 (0.9)
Stage IV	22 (16.1)	19 (21.6)	10 (22.7)	5 (10.2)	56 (17.6)

A surgical procedure was performed, either for biopsy and diagnosis or for surgical extirpation and treatment, in 74.2% of patients. Surgical procedures were analyzed by the total number of times a procedure was performed, as a small proportion of patients had more than one surgical procedure performed. Modified radical mastectomy was the most commonly performed procedure (165 times) followed by simple mastectomy (45 times) and excisional biopsy (20 times). Simple mastectomy was frequently performed as a palliative operation in the setting of locally advanced disease in patients with known or likely metastases. Performing a breast operation in patients with distant metastatic disease will not generally change the ultimate outcome of the disease (i.e. death), particularly in Ethiopia where chemotherapy is difficult to obtain. The alleviation of symptoms (e.g., pain, bleeding, malodor) caused by a burdensome breast mass is the primary goal (i.e. palliation) when operating on a patient with metastatic disease. A number of patients in whom biopsies (e.g., excisional biopsy) were performed were lost to follow-up and never received notification of a cancer diagnosis or definitive surgical and adjuvant therapy.

Due to the centralized and limited availability of chemotherapy and radiotherapy in a single center (Tikur Anbessa Hospital, Addis Ababa) and the very limited long-term follow-up of patients, these therapies were analyzed based only on whether a referral occurred. Official referral for treatment required the completion of several Ministry of Health documents, which did not in any way guarantee receipt of treatment. In total, 87 (27.4%) patients were referred for either adjuvant or palliative chemotherapy and 55 (17.3%) patients were referred for either adjuvant or palliative radiotherapy. Several patients were explicitly referred for both modalities are represented in each proportion. Endocrine therapy with the selective estrogen receptor modulator tamoxifen is sporadically done in Ethiopia despite the absence of any estrogen or progesterone receptor staining on pathologic specimens. A total of 32 (10.1) patients were confirmed to have initiated endocrine therapy with tamoxifen.

As mentioned previously, long-term follow-up with patients was significantly limited in the Ethiopian context and many patients were never seen after discharge from outpatient clinic or inpatient hospitalization at time of diagnosis. Despite an active approach to follow-up whereby all patients with a phone number available in their hospital chart were called to ascertain new details of their disease since discharge from the hospital, follow-up for patients was a mean of only 8.5 months (255 days) and a median of only 1.4 months (42 days). During this follow-up period, 32 patients (10.1%) were found to have died from breast cancer and 30 patients (9.4%) were noted to have findings of local or regional recurrence of their disease. It is very likely that many more patients experienced events such as death or recurrence, however due to the limited duration of follow-up, determining this information was not possible.

REGISTRY ESTABLISHMENT PROCESS

After 10 months of intensive involvement, we have established one of the first cancer registries in Ethiopia with a sustainable, low-cost registry model. Four hospitals were joined in this registry which included urban and rural as well as public and private institutions. Across these institutions, a total of five registrars and one project manager were fully trained in the science of breast cancer registration while another four peripheral registry staff were trained in various key aspects of cancer registration required to perform their duties (e.g., data entry into CanReg5). Prospective registrations efforts are ongoing and based on the initial grants obtained (i.e. without the outlay of any additional funding), ought to continue for the next three years. At that time, the future sustainability of the registry will likely depend on the willingness of the hospital administration to continue these activities, or on the success of obtaining additional grant funding focused on sustaining the registry's work.

While cancer registries have been successfully established and implemented in other sub-Saharan African countries, there were distinct challenges in the institutions in which we worked and the Ethiopian context at-large. These challenges were primarily related to documentation, pathology resources, funding, and patient follow-up.

Clinical records and documentation were some of the most challenging hurdles to overcome. In all of the hospitals, patient charts were difficult to locate and greatly lacking in detail. As shown previously in Figure 3, the organization of charts in storage rooms was typically nonexistent and, in the absence of adequate shelving, charts were strewn across any flat surface, most often the floor. Due to the difficulty of locating charts in such conditions, patients who returned for follow-up would often have to have a second or even third chart made new for them at each visit. Therefore, locating a single chart for a patient did not ensure that the entire clinical record for that patient was present. The records themselves often contained very little information about the patients' disease with critical portions of the history, physical exam, or other aspects of the clinical record necessary for staging entirely missing. This required that staging variables often be left blank in the absence of reliable data. At one hospital, patients' clinical records were called "cards" rather than charts because the entire record of all examinations, diagnoses, procedures, and follow-ups for that patient were contained on the front and back of a half sheet of A4 sized cardstock (10.5 x 14.9 cm). Within the past year, however, the Ministry of Health announced mandatory utilization of a larger, standardized, and more comprehensive hospital chart to be used for all patients in all health facilities. In each hospital, the principal investigator also initiated discussions with chief medical staff to improve data quality and quantity across the hospital; in most hospitals, the research team and registrars assisted with the organization of chart storage rooms; and in one hospital, the research team funded the actual purchase of shelving for chart organization.

Pathologists and pathologic diagnoses, as previously addressed, are difficult to come by in Ethiopia, which has approximately 12 pathologists in the entire country. None of the hospitals in which we worked had in-house pathologists and all specimens were sent to central pathology laboratories, which required sending specimens a significant distance to Addis Ababa for the three hospitals in the Wolayita Zone (SCH, OWSH, & DSM). Turnaround time for pathologic examination at private pathology clinics was on the order of 4-10 weeks, if results were received at all. Biopsy specimens were often lost or ruined in transport and the hand-written pathology reports often never made it back to the pathology logbooks or patients' charts at the hospitals from which the specimens came. Additionally, most pathology labs were unwilling, due to an incredible workload, to perform complete gross examination of surgical specimens (ie. whole mastectomy specimens with all axillary lymph nodes) and required that partial specimens be submitted in containers measuring no larger than approximately 6x8 cm. The information in pathology reports was often poor quality and incomplete due to rudimentary staining capabilities and the absence of standard system for reporting high quality results. This is at least partially exemplified by the low proportion of specimens with a histologic grade reported (see Table 6). Estrogen receptor (ER) and progesterone receptor (PR) staining were also not available at any pathology lab in the country. For several years, starting in 2005, the antibodies required for ER/PR staining were donated and brought into the country through a project funded by Astra Zeneca, the pharmaceutical company that produces tamoxifen. However since this project ended, the antibodies are no longer available in Ethiopia (Reeler et al., 2008).

In the resource limited environment of LMICs, there is, by definition, a relative lack of funding for activities such a biomedical research. While physicians and staff in each hospital provided clear and ardent support of the breast cancer registration activities, they also made it clear that breast cancer was only one of many pressing health problems. Everything required for registry implementation, from inexpensive photocopies of abstraction forms to the salaries of registrars, was paid for using research funds. Participating hospitals did not share any costs, despite the benefit these data and data systems could provide to hospitals and their patients. For most hospitals, establishing cancer registration was the first effort to systematically track patients and perform epidemiologic research. In so doing, the hospitals benefited from better organized medical records; knowledge of patient disease characteristics, treatment patterns and outcomes in a given facility; a research system and staff capable of expanding into other research endeavors; and data which clearly underscores the need for increased resources to treat cancer in each of these hospitals. Each of these benefits, most importantly, provides an opportunity to improve upon the quality and quantity of care that patients receive. However, the lack of “buy in” from participating institutions posed a threat to the sustainability of cancer registration in these hospitals. Therefore, we applied for and were granted further research funding that will allow this project to continue for at least three more years, after which time we will be required to pursue further funding mechanisms.

Patient follow-up, or the relative lack thereof, will be a major barrier to measuring outcomes and survival as this registration project continues. As demonstrated by the short median follow-up in Table 6, the last date of contact with breast cancer patients is frequently the date of discharge from clinic or inpatient hospitalization. There are many potential reasons for the high proportion of patients quickly lost to follow-up and this will require further investigation to improve. When possible, we used telephone communication to actively follow-up with patients. Telephone numbers, however, were infrequently recorded in patients' charts, particularly in the three rural hospitals. Unlike many countries in sub-Saharan Africa, the telecommunication system for mobile and landline telephones is a government-owned monopoly. There has been very low penetration of the mobile telecommunication market into Ethiopia, particularly in rural areas where there is also no existing infrastructure for landline telephones. In 2012, the mobile phone penetration into Ethiopia was one of the lowest in Africa at approximately 21.8%, which is very low compared with 47.4% in Rwanda, 69.8% in Kenya, or 98.1% in the United States (International Telecommunications Union, 2012). Actively calling patients to follow up at regular intervals is therefore impossible for many patients due to the lack of telecommunication infrastructure. The situation is complicated by the way in which people denote the location of their residence. There are very few named streets in Ethiopia and while there is a system for numbering houses in a geographic region, most patients do not know the number of their house. Patients' addresses are therefore typically listed nonspecifically as a region populated by thousands or tens of thousands of people. The fact that visiting patients' homes would likely be prohibitively expensive in a project of this size is irrelevant due to the fact that patients' homes would not be able to be readily located.

CHAPTER 5: DISCUSSION

The data presented here represent some of the first direct epidemiological findings from a cancer registry to come from Ethiopia. A multi-institutional breast cancer registry has been established and has documented one of the first glimpses into the current status of breast cancer diagnosis and care in Ethiopia. While the initial cohort is relatively small, enrolling 318 patients in the first year of operation is significant contribution and the feasibility of a registry has been established using a sustainable framework. Ongoing patient enrollment will allow for expanded analysis in the years to come.

The current findings reveal a much younger median age at diagnosis (40 years) when compared with the median age of 61 years when women tend to be diagnosed in the United States (Howlader et al., 2012). This finding is most likely related to the presence of a younger population rather than a pathologically distinct form of breast cancer. The wide-based population pyramid for Ethiopia, shown in Figure 2, illustrates the skewed age of the population, where the median age is 17.5 years and life expectancy is only 60 years (United States Central Intelligence Agency, 2012). Projections of population growth and aging, in conjunction with a more Westernized diet and lifestyle, in the coming 20-30 years in LMICs are among the reasons that the burden of cancer in these countries is expected rise. Cancer incidence in high income countries occurs most commonly in aging populations, generally after age 50 to 60 years.

The current findings also document a significant delay in presentation where men and women took a mean of 15.0 months, or a median of 12 months, to present for diagnosis after noticing breast-related symptoms. As a component of the AstraZeneca-funded Axios International Ethiopia Breast Cancer Project, Dye et al. (2012) reported on the initial symptoms of breast cancer that led individuals to pursue some form of care. The initial symptom which triggered action was most commonly a breast lump (82.6%) followed by an itching or burning sensation (11.6%) and pain (1.4%). Similar to this cohort, they found that patients “ignored” their symptoms for an average of 1.6 years before taking some form of action (Dye et al., 2012). Whether the delay in presentation was caused by patients “ignoring” symptoms or not having resources or ability to pursue care is contentious. Barriers that delay or prevent individuals, particularly women, from pursuing healthcare in Ethiopia have been documented in numerous studies. Some of the obstacles include out-of-pocket costs, excessive distance from home/no available transportation, facility not open or adequately staffed, poor quality of service, no female health provider, not customarily done in their culture, and prohibition by husband and/or family (Ethiopia Central Statistical Agency & ICF International, 2012; Mekonnen & Mekonnen, 2003; Melese, Alemayehu, Friedlander, & Courtright, 2004). In a separate study, Dye et al. (2011) related that Ethiopian women diagnosed with breast cancer report a lack of knowledge about breast cancer, some never having heard of the disease, or a lack of knowledge of breast cancer treatments as prevailing barriers to pursuing care. Study participants, both male and female, described a conspicuous sense of fatalism and hopelessness for those diagnosed with cancer, firmly believing that breast cancer is a “killer” and that it cannot be cured (De Ver Dye et al., 2011). More than likely, a combination of physical and health system barriers mixed with people’s beliefs, or lack thereof, about cancer serve as the basis for the significant delays in presentation observed in our cohort.

What is clear from these results is that the delay in presentation, coupled with the inability to screen for breast cancer mammographically, results in a late stage at diagnosis, much later than is seen in more resourced settings. Largely through the establishment of screening mammography, tremendous strides have been made in detecting *in situ*, or pre-invasive, breast cancers that are much more likely to be curable, thereby significantly improving long-term survival. In this cohort of Ethiopian patients, where there are no screening programs for breast cancer using mammography, not a single case of *in situ* cancer (Stage 0) was diagnosed. In addition, providers who might be screening for breast cancer systematically using clinical breast exams are also unavailable in Ethiopia. Thus, more than 70% of patients enrolled in the registry were diagnosed with Stage III (53.4%) or Stage IV (17.6%) late stage disease. The median stage at presentation was Stage IIIB, which represents the start of later-stage disease. Figure 5 clearly demonstrates the disparity in stage at diagnosis between this Ethiopian cohort and patients diagnosed with breast cancer in North America during a similar time period (Copeland et al., 2013). The median stage at diagnosis in North America was Stage I and more than 80% of patients were diagnosed before reaching Stage III (i.e. Stages 0, I, and II), signifying earlier stages when the disease is imminently more curable. Diagnosing breast cancer at the earliest stage possible, e.g. stage 0 or I, is critical to improving the outcomes associated with this disease in Ethiopia and other LMICs where screening programs with mammography are currently unavailable.

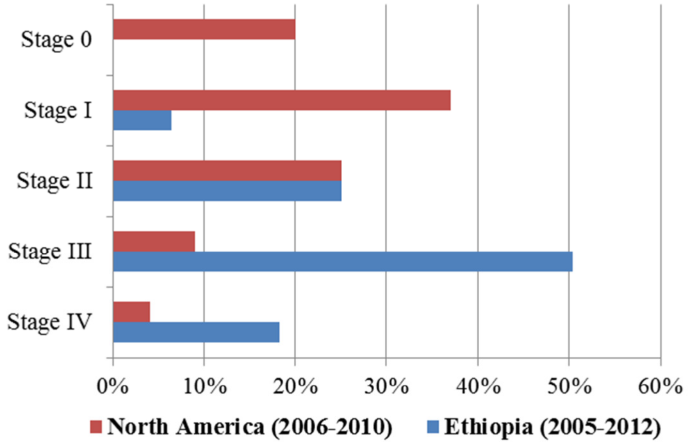

Figure 5. Stage at Diagnosis for Incident Ethiopian and North American Breast Cancer Cases. Adapted from Combined Cancer Incidence for the United States, Canada, and North America (Vol. I), by G. Copeland, et al., 2013, Springfield, IL: North American Association of Central Cancer Registries, Inc. Copyright 2011 by North American Association of Central Cancer Registries, Inc.

Surgery served as a mainstay of treatment for breast cancer diagnosed in this cohort with nearly 75% of patients receiving some form of surgical procedure, either for tissue diagnosis, treatment, or both. Surgical cure of breast cancer is possible in cases where diagnosis is accomplished early and extirpation occurs prior to locoregional spread. Surgery performed after spread to regional or distant lymph nodes has been demonstrated to provide survival benefit when accompanied by an appropriate regimen of neoadjuvant or adjuvant chemotherapy and radiotherapy. In the Ethiopian context where chemotherapy and radiotherapy are only available to the general population at a single center, and are exorbitantly expensive, the likelihood of receiving neoadjuvant or adjuvant therapy is exceptionally low. In our cohort, analysis was only possible based on referral for adjuvant therapy, since initiation of therapy was unknown without records from Tikur Anbessa Hospital, the one site in the country where chemotherapy and radiation therapy are currently delivered.

Until adjuvant therapy is more widely available, the best chance for curative treatment and long-term survival is surgical resection in early stage disease. Unfortunately, early stage disease is rarely diagnosed, as shown above. The effectiveness of surgery is limited by the late stage at diagnosis and is often performed as a palliative procedure for women suffering due to an ulcerated, fungating, malodorous, and frequently bleeding breast mass. Furthermore, there are relatively few surgeons in Ethiopia (approximately 1 surgeon for every 360,000) and the distribution of surgical capacity is primarily centered around the capital city. Receipt of a timely cancer operation is not likely, particularly in rural areas, when surgical resources are limited and backlogs require the scheduling of operations months in advance. The long delays in receipt of surgery, after the reported long delays in initial presentation of the primary breast tumor, translates to few cases that are truly curable at time of surgery. Developing surgical capacity, as well as assuring a more equitable geographic distribution of surgeons, will be a key facet that must be incorporated into any future cancer control strategy.

Gebremedhin and Shamebo (1998) published the first and only study with which the current findings can be plausibly compared. While their study documents patients who presented to Tikur Anbessa Hospital nearly 20 years ago, their results are staggeringly similar to those presented here. They, too, found a young cohort of men (mean 52.1 years) and women (mean 41.8 years) who presented after the exact same long period of breast-related symptoms (median 12 months) with advanced disease (76% with Stage III or IV). Moreover, their comments about the frequent international travel of patients to obtain cancer treatment due to the sporadic availability of domestic surgical and adjuvant treatment largely hold true today. Despite their conclusion that Ethiopia must be equipped with the necessary means to diagnose and treat breast cancer, it seems that very little has changed over the past 15 years. Breast cancer was a devastating clinical problem at the time of publication and, while significant interval progress has been made in areas of communicable disease, their nearly identical results suggest that cancer has still not made it onto the health agenda in Ethiopia.

As the burden of cancer, particularly breast cancer, is projected to rise in LMICs in coming years, it is essential that programs for cancer control be established and that they be based on a sound understanding of the burden of cancer in a given country (Anderson et al., 2011; Mamudu, Yang, &

Novotny, 2011; D. M. Parkin, 1994; World Health Organization, 2011). Knowledge of the burden and epidemiology of breast cancer in Ethiopia, and much of sub-Saharan Africa, remains poor in the relative absence of programs in cancer epidemiology or registration. In numerous publications and recommendations the WHO has maintained that cancer registration must be a central and initial component of any country's cancer control program (World Health Organization, 2002; World Health Organization & International Atomic Energy Agency, 2011). It is important that a resource-constrained country like Ethiopia carefully weigh the many pressing health needs among their population. Those involved in health ministries and health policy formulation can only ensure proper and equitable allocation of resources when there is adequate data available regarding the competing disease burdens in the populations they serve. While communicable diseases have rightly received the lion's share of attention and funding to-date in LMICs, the projected shift in disease burden must be accompanied by new efforts to quantify and address the largely unaddressed and commonly fatal problem of cancer.

Rather than proceeding directly with interventions in breast cancer screening or treatment, which are recognized clinically as desperately needed, we chose to start with the foundational work of establishing a program of cancer registration. We would argue that the development of tumor registries is an essential component for assessing the scope and detail of breast cancer epidemiology, thus making registries pivotal for the long-view of sustained involvement in future projects improving breast cancer screening, treatment, and control in the country. Cancer registries have often been perceived as a luxury available only to high-income countries with the means to establish a program of national population coverage. At this stage of cancer control program development in Ethiopia, some have advocated that there is clearly a role for the establishment of hospital-based cancer registries, including IARC, the UN, and the WHO (South Africa National Cancer Registry., 1995; World Health Organization, 2011; World Health Organization & International Agency for Research on Cancer, 2013a). In the absence of population-based registries, hospital-based registries are able to provide the initial source of epidemiologic data on cancer patients and potentially lead to the establishment of a population-based registry through integration with other health facilities and data sources in a defined population (Valsecchi & Steliarova-Foucher, 2008). Since cancer diagnosis and care is often restricted to relatively few medical institutions in Ethiopia, the case may be made that hospital-based registries can serve as a viable source for the epidemiology and burden of disease affecting large segments of the overall population.

We have performed this initial step of establishing hospital-based breast cancer registries in four hospitals in Ethiopia, one hospital in the capital city and three rural hospitals in the geographically defined Wolayita Zone of Southern Ethiopia. A number of barriers were encountered as we established these registries. From the literature, it seems that some of these barriers are common in low-resource settings, although others may likely be unique to the Ethiopian context. Several barriers related to documentation, pathology resources, funding, and patient follow-up were discussed in the results section and Table 8 below summarizes all of the pertinent barriers which we confronted. We present this table acknowledging that our future efforts, and hopefully the efforts of others, will need to take these barriers into consideration as cancer epidemiology and subsequent cancer control programs in Ethiopia are developed. Note that these are barriers to registry establishment and a host of distinct treatment and survival related barriers also exist.

This study has several limitations which ought to be considered when interpreting the results. First is the difficulty we experienced with case finding. As previously discussed, passive case finding or formal reporting were not options in this context and active case finding require the scouring of many different logbooks and resources in each hospital. Such a system is prone to incomplete case finding and is further exacerbated by the difficulties we experienced subsequently when trying to find charts in disheveled medical record storage rooms. It is not possible to know exactly how many cases were missed during case finding, but it is safe to assume that cases were missed and this number of cases is certainly only a fraction of the breast cancer patients seen at these four hospitals over a 7.5 year period. Partially due to incomplete case finding, there is a small number of patients presented in this cohort. We have presented a preliminary cohort of small sample size from a collection of hospital-based registries without any pretense of population coverage. While descriptive statistical analysis, as presented here, represents significant new data regarding breast cancer, it is insufficient for drawing conclusions regarding incidence or mortality and more complex statistical modeling is not possible without a larger sample and greater detail and duration of long-term follow-up. The short duration of follow-up is, in itself, a limitation of this study that prevents substantive analysis of treatment outcomes and long-term survival. Regarding the model of registry establishment, this project was led by a principal investigator who lived on site for nearly one year and was almost exclusively engaged in this work. There are limited opportunities to replicate such a scenario where dedicated international research time and funding are available to a researcher and/or trainer.

Table 8. Barriers Related to Breast Cancer Registry Establishment in Ethiopia

Patient-related Factors	- Poor, or complete lack of, insight regarding cancer as a disease, the need for early diagnosis, and/or the availability of cancer treatment among the population in Ethiopia - Frequent fatalism and sense of hopelessness that prevents timely presentation for care - Significantly constrained personal economic resources and high individual opportunity cost of pursuing healthcare - Widespread acceptance and uptake of traditional healers over modern medical care - Largely rural population (83%) requiring significant travel to reach hospitals and health facilities resulting in delay in presentation and/or follow-up
Cancer-related Factors	- Limited pathologic diagnoses of cancer secondary to very few pathologists, frequently missing pathology reports, and the overall poor/rudimentary quality of pathologic evaluation - Absence of immunohistochemistry staining (ie. ER/PR status), molecular studies, and tissue banking - Potential under-staging of breast cancers due to partial pathologic specimen submission and, therefore, incomplete analysis (e.g. absence of data regarding tumor size, nodal involvement, or actual number of positive nodes) - Small consortium of cancer-related specialists (four medical oncologist, one radiation oncologist, and no surgical oncologist) in the entire country - Minimal interest or productivity in domestic cancer-related research
System-related Factors	- No national or subnational program for breast cancer screening - Significant healthcare worker shortages (e.g., physicians, surgeons, nurses) - Poor organization and inadequate documentation in health facilities - Paucity of reliable and accurate data sources in healthcare delivery - Absence of standard system for death certification - Limited domestic resources and funding available for sustained programs in cancer registration - Poor health system performance - Health system that remains centered around communicable disease and dependent upon international aid and funding

CHAPTER 6: CONCLUSION AND FUTURE DIRECTION

Globally, breast cancer is the most commonly diagnosed cancer among women. The highest incidence rates of breast cancer are effectively concentrated in Western, high-income countries while the incidence rates in much of Sub-Saharan African have remained low. The burden of cancer in LMICs, however, is expected to rise precipitously in the coming decades as their populations grow and age and individuals adopt more westernized diets and lifestyles. While communicable diseases have dominated the burden of disease in Ethiopia in the past, noncommunicable diseases such as cancer are on the rise and will soon be among the most pressing needs in the health system. There is no national cancer control strategy in Ethiopia and the limited cancer-related health infrastructure available is already overwhelmed with the current burden of disease.

As expected in a country with no breast cancer screening program, the distribution of cancer stage at diagnosis is much later than observed in more resourced countries. Patients with breast cancer in Ethiopia are young and typically present long after detecting breast-related symptoms. By the time of diagnosis, late-stage disease (Stage III/IV) has developed in more than 70% of patients, which is contrary to what is found in Western, high income countries where less than 20% of patients have late-stage disease at the time of diagnosis. Obtaining microscopic verification of breast cancer diagnoses will remain difficult until there is increased and more equitably distributed pathologic examination available in the country. Surgical and adjuvant therapies are not readily available and outcomes for breast cancer, a cancer which is treatable and often has excellent outcomes in more resourced settings, remain dismal. Unfortunately, our ability to track these long-term outcomes has been limited by short follow-up and a lack of infrastructure (e.g., telecommunications) to support various forms of active follow-up. Systematic changes in the ways that breast cancer is screened, diagnosed, treated, and surveilled must occur if the impact of this disease in Ethiopia is to improve.

Current knowledge of the breast cancer burden and epidemiology in Ethiopia remains poor and prior estimates of key statistics like incidence and mortality have been extrapolated from studies performed in other countries. Development of tumor registration is essential to accurately assess the scope and detail of breast cancer incidence, staging, and mortality in Ethiopia and other low- or middle-income countries. Registries enable monitoring of cancer stage, treatment patterns, and outcomes which can then be used to inform policies and design and evaluate programs of breast cancer prevention, screening, diagnosis, and treatment.

While we have established the first known multi-institutional breast cancer registry in the country of Ethiopia, epidemiologic cancer research must be increased to include population-based registries. From this registry has come an initial indication of the severity of the problem of breast cancer in the country. Establishing the registry was accompanied by numerous challenges and barriers which included a combination of patient-related, cancer-related, and system-related factors. Strategies to address and overcome each barrier were incorporated into this model for registry development, and may, in turn, serve as a model for other registries to be implemented in sub-Saharan Africa. These hospital-based registries are an essential first step toward improving cancer epidemiology in the country; however, population-based registries are urgently needed in order to cover a greater proportion of the population and determine an accurate incidence of breast cancer from data gathered within the country. The overall health policy goal must be to develop capacity to produce reliable, high-quality information on the burden of cancer in order to design and implement a comprehensive national strategy for cancer control that will be developed, implemented, and evaluated at all levels within the health system.

This thesis summarizes the very beginning of what we hope is a long involvement in breast cancer and cancer control in Ethiopia. The funding we have received in support of the tumor registry to-date is projected to last for approximately three years. Enrollment and registration of patients diagnosed with breast cancer is currently ongoing at all four hospitals (Myungsung Christian Medical Center, Soddo Christian Hospital, Otona Wolayita Soddo Hospital, and Dubbo St. Mary Catholic Hospital) through the efforts of the registrars and project manager trained through this project. It is our hope that, as this registration project matures and further funding is secured, we will be able to organize a population-based cancer registry that reports on all breast cancer diagnoses in the Wolayita Zone. In addition to cancer registration, we also hope to broaden the scope of our involvement in breast cancer. Future efforts will likely include efforts related to secondary prevention and early detection. Two primary goals will be to:

a. train community health care workers in the clinical breast exam, with the ancillary benefit of raising awareness of breast cancer among health practitioners, and
b. investigate the availability and utilization of mammography in the country.

We have shown that the status of breast cancer screening, diagnosis, and treatment, as well as the stage at diagnosis, have remained essentially unchanged over the past 15 years. If older studies focusing on breast cancer had been performed or published, they, too, would likely provide evidence that the situation for women and men diagnosed with breast cancer has not improved in many years. Breast cancer is a disease that has seen comprehensive changes in its management and dramatic improvements in its survival over the past 50 years in many countries more resourced that Ethiopia. It is our steadfast goal to collaborate in the sweeping changes that must occur in Ethiopia to accomplish favorable stage migration and improved survival through the strategic formulation and implementation of a program for national cancer control. Our data presented in this thesis must be the first of many projects to define the growing burden of cancer in Ethiopia and attempt to quantify the need for drastically improved cancer care.

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APPENDIX

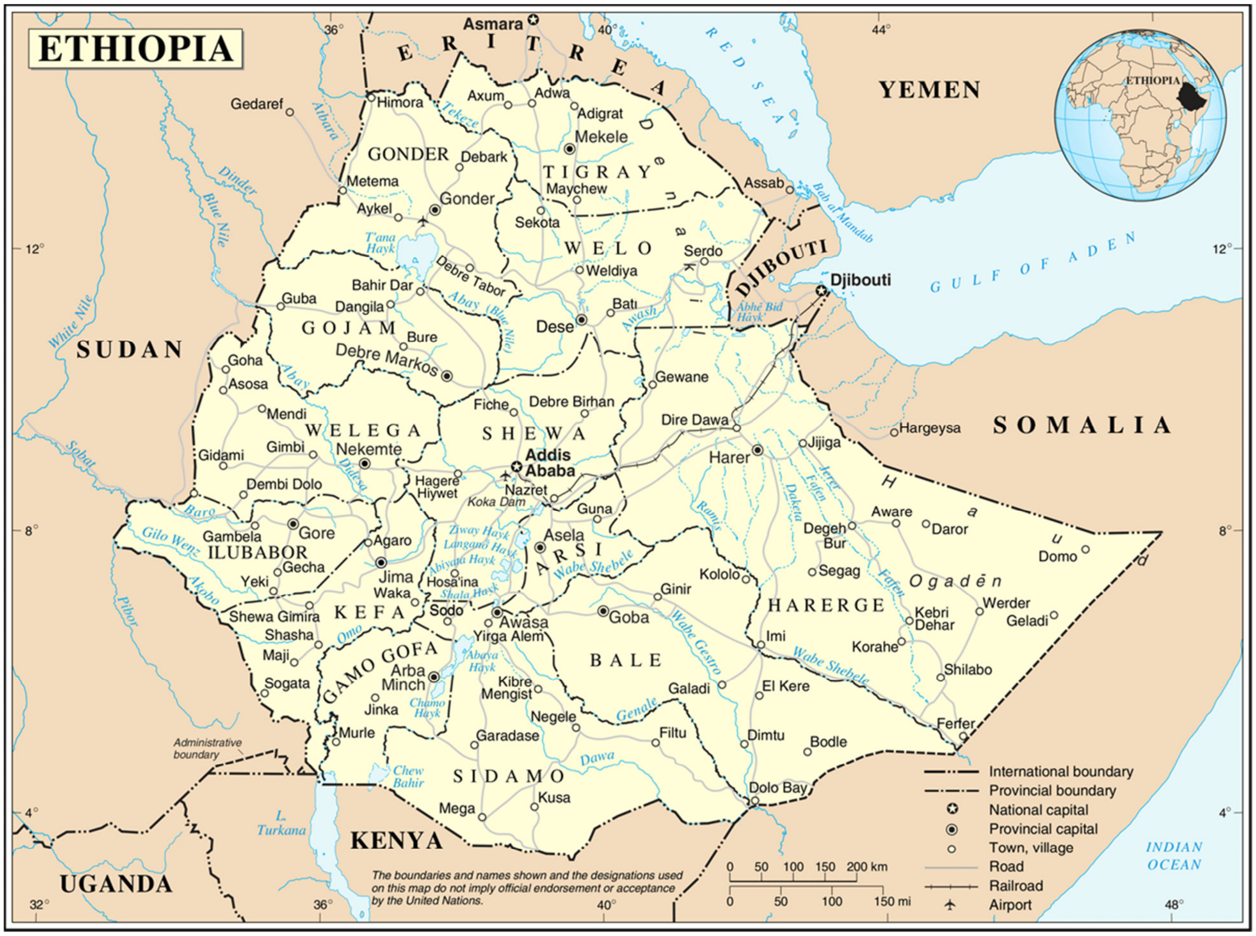


Figure 1. Map of Ethiopia including Subset Africa Map. Reprinted from Ethiopia Maps in MapsOf.net. Retrieved July 27, 2013, from http://mapsof.net/ethiopia. Copyright 2013 by Creative Commons Attribution-ShareAlike.

Figure 2. Map of Ethiopia Depicted with Constituent Regions and Special City Administrations. Reprinted from Ethiopia Maps in MapsOf.net, Retrieved July 27, 2013, from http://mapsof.net/ethiopia. Copyright 2013 by Creative Commons Attribution-ShareAlike.

Figure 3. Southern Nations, Nationalities, and Peoples Region Subdivided by Zone. Reprinted from Ethiopia's Rural Facilities and Services Atlas: SNNP Regional State, Vol. VII (p. 9), 2011, Addis Ababa, Ethiopia: Ethiopia Central Statistical Agency. Copyright 2011.

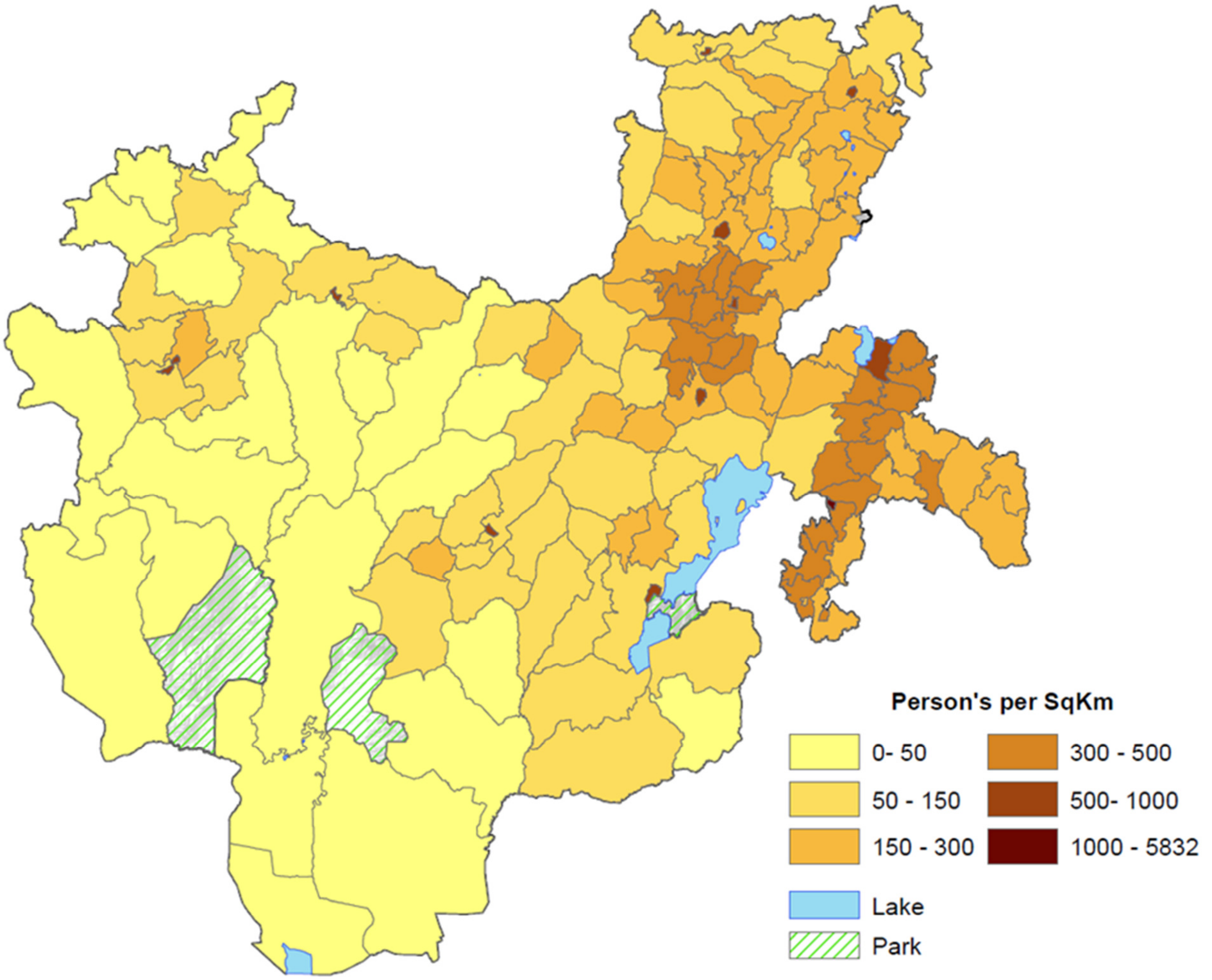


Figure 4. Southern Nations, Nationalities, and Peoples Region Population Density. Reprinted from Ethiopia's Rural Facilities and Services Atlas: SNNP Regional State, Vol. VII (p. 16), 2011, Addis Ababa, Ethiopia: Ethiopia Central Statistical Agency. Copyright 2011.

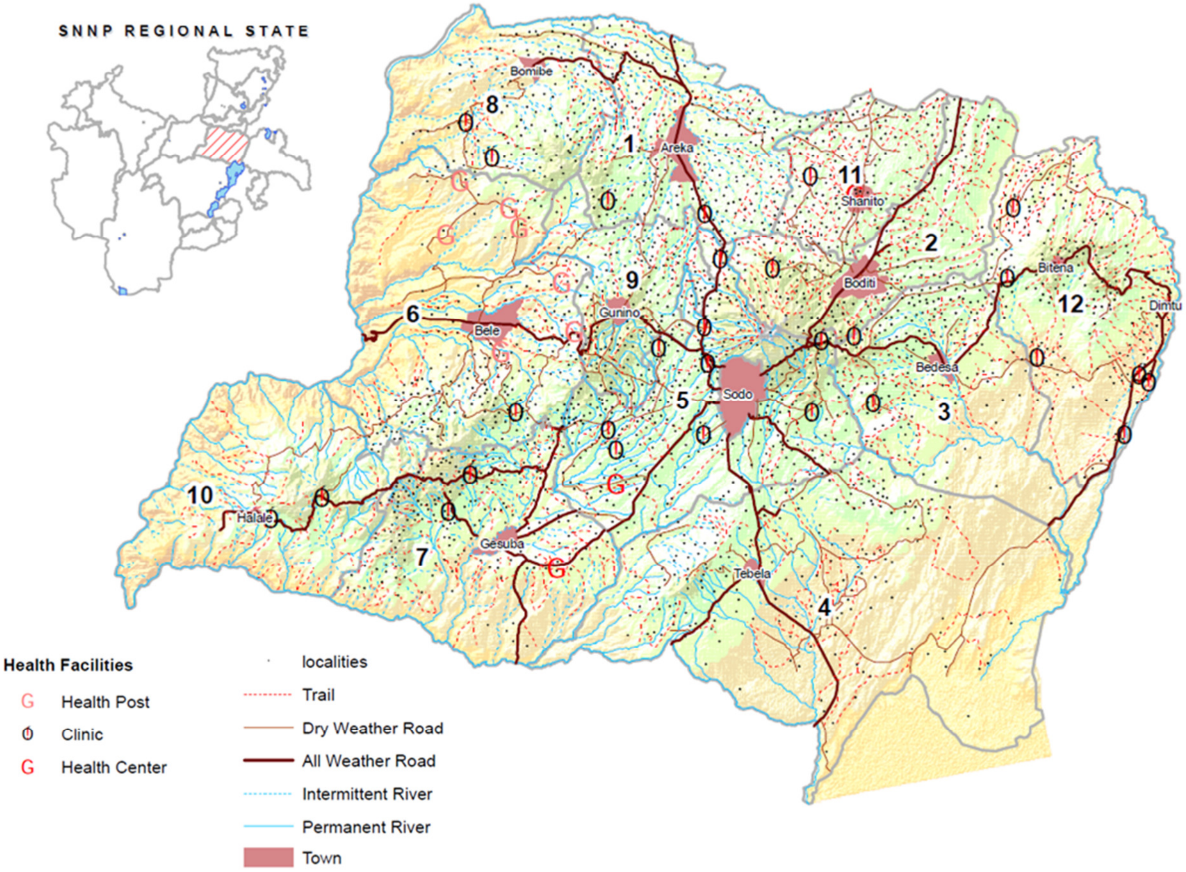
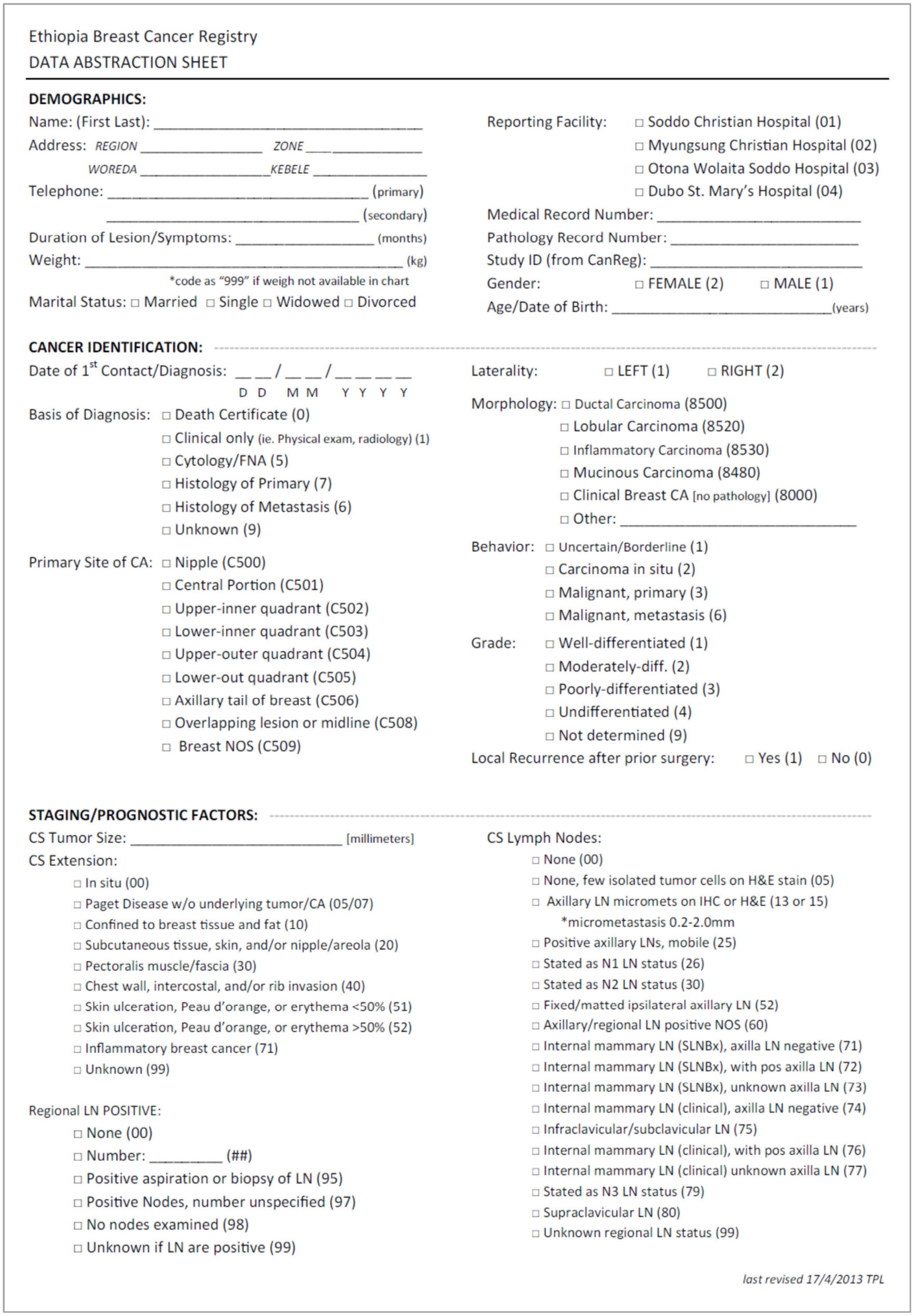


Figure 5. Wolayita Zone Health Facilities. Reprinted from Ethiopia's Rural Facilities and Services Atlas: SNNP Regional State, Vol. VII (p. 47), 2011, Addis Ababa, Ethiopia: Ethiopia Central Statistical Agency. Copyright 2011.

The Wolayita Zone population consists of approximately 1,425,062 individuals, of which 93.2% (1,328,598 people) live in a rural area. This map demonstrates the distribution of health facilities within the Wolayita Zone. The official hierarchy of health facilities in Ethiopia specified by the Ministry of Health, progressing from smallest to largest, includes: health posts, health clinics, health centers, and hospitals (Ethiopia Central Statistical Agency, 2011).

Note that no hospitals are shown in the zone, including the three hospitals in which breast cancer registries were established, Soddo Christian Hospital (Sodo), Otona Wolayita Soddo Hospital (Sodo), and Dubo St. Mary’s Catholic Hospital (Areka). This likely depicts a significant lag in data reporting as all three hospitals were established within the past ten years.



Ethiopia Breast Cancer Registry
DATA ABSTRACTION SHEET

DEMOGRAPHICS:

Name: (First Last): ________________________________
Address: *REGION* ______________ *ZONE* ______________
WOREDA ______________ *KEBELE* ______________
Telephone: ______________________________ (primary)
______________________________ (secondary)
Duration of Lesion/Symptoms: ________________ (months)
Weight: ______________________________________ (kg)
*code as "999" if weigh not available in chart
Marital Status: ☐ Married ☐ Single ☐ Widowed ☐ Divorced

Reporting Facility:
☐ Soddo Christian Hospital (01)
☐ Myungsung Christian Hospital (02)
☐ Otona Wolaita Soddo Hospital (03)
☐ Dubo St. Mary's Hospital (04)

Medical Record Number: ________________________
Pathology Record Number: ______________________
Study ID (from CanReg): ________________________
Gender: ☐ FEMALE (2) ☐ MALE (1)
Age/Date of Birth: __________________________(years)

CANCER IDENTIFICATION:

Date of 1st Contact/Diagnosis: __ __ / __ __ / __ __ __ __
D D M M Y Y Y Y

Basis of Diagnosis:
☐ Death Certificate (0)
☐ Clinical only (ie. Physical exam, radiology) (1)
☐ Cytology/FNA (5)
☐ Histology of Primary (7)
☐ Histology of Metastasis (6)
☐ Unknown (9)

Primary Site of CA:
☐ Nipple (C500)
☐ Central Portion (C501)
☐ Upper-inner quadrant (C502)
☐ Lower-inner quadrant (C503)
☐ Upper-outer quadrant (C504)
☐ Lower-out quadrant (C505)
☐ Axillary tail of breast (C506)
☐ Overlapping lesion or midline (C508)
☐ Breast NOS (C509)

Laterality: ☐ LEFT (1) ☐ RIGHT (2)

Morphology:
☐ Ductal Carcinoma (8500)
☐ Lobular Carcinoma (8520)
☐ Inflammatory Carcinoma (8530)
☐ Mucinous Carcinoma (8480)
☐ Clinical Breast CA [no pathology] (8000)
☐ Other: ____________________________

Behavior:
☐ Uncertain/Borderline (1)
☐ Carcinoma in situ (2)
☐ Malignant, primary (3)
☐ Malignant, metastasis (6)

Grade:
☐ Well-differentiated (1)
☐ Moderately-diff. (2)
☐ Poorly-differentiated (3)
☐ Undifferentiated (4)
☐ Not determined (9)

Local Recurrence after prior surgery: ☐ Yes (1) ☐ No (0)

STAGING/PROGNOSTIC FACTORS:

CS Tumor Size: ________________________ [millimeters]

CS Extension:
☐ In situ (00)
☐ Paget Disease w/o underlying tumor/CA (05/07)
☐ Confined to breast tissue and fat (10)
☐ Subcutaneous tissue, skin, and/or nipple/areola (20)
☐ Pectoralis muscle/fascia (30)
☐ Chest wall, intercostal, and/or rib invasion (40)
☐ Skin ulceration, Peau d'orange, or erythema <50% (51)
☐ Skin ulceration, Peau d'orange, or erythema >50% (52)
☐ Inflammatory breast cancer (71)
☐ Unknown (99)

Regional LN POSITIVE:
☐ None (00)
☐ Number: _________ (##)
☐ Positive aspiration or biopsy of LN (95)
☐ Positive Nodes, number unspecified (97)
☐ No nodes examined (98)
☐ Unknown if LN are positive (99)

CS Lymph Nodes:
☐ None (00)
☐ None, few isolated tumor cells on H&E stain (05)
☐ Axillary LN micromets on IHC or H&E (13 or 15)
*micrometastasis 0.2-2.0mm
☐ Positive axillary LNs, mobile (25)
☐ Stated as N1 LN status (26)
☐ Stated as N2 LN status (30)
☐ Fixed/matted ipsilateral axillary LN (52)
☐ Axillary/regional LN positive NOS (60)
☐ Internal mammary LN (SLNBx), axilla LN negative (71)
☐ Internal mammary LN (SLNBx), with pos axilla LN (72)
☐ Internal mammary LN (SLNBx), unknown axilla LN (73)
☐ Internal mammary LN (clinical), axilla LN negative (74)
☐ Infraclavicular/subclavicular LN (75)
☐ Internal mammary LN (clinical), with pos axilla LN (76)
☐ Internal mammary LN (clinical) unknown axilla LN (77)
☐ Stated as N3 LN status (79)
☐ Supraclavicular LN (80)
☐ Unknown regional LN status (99)

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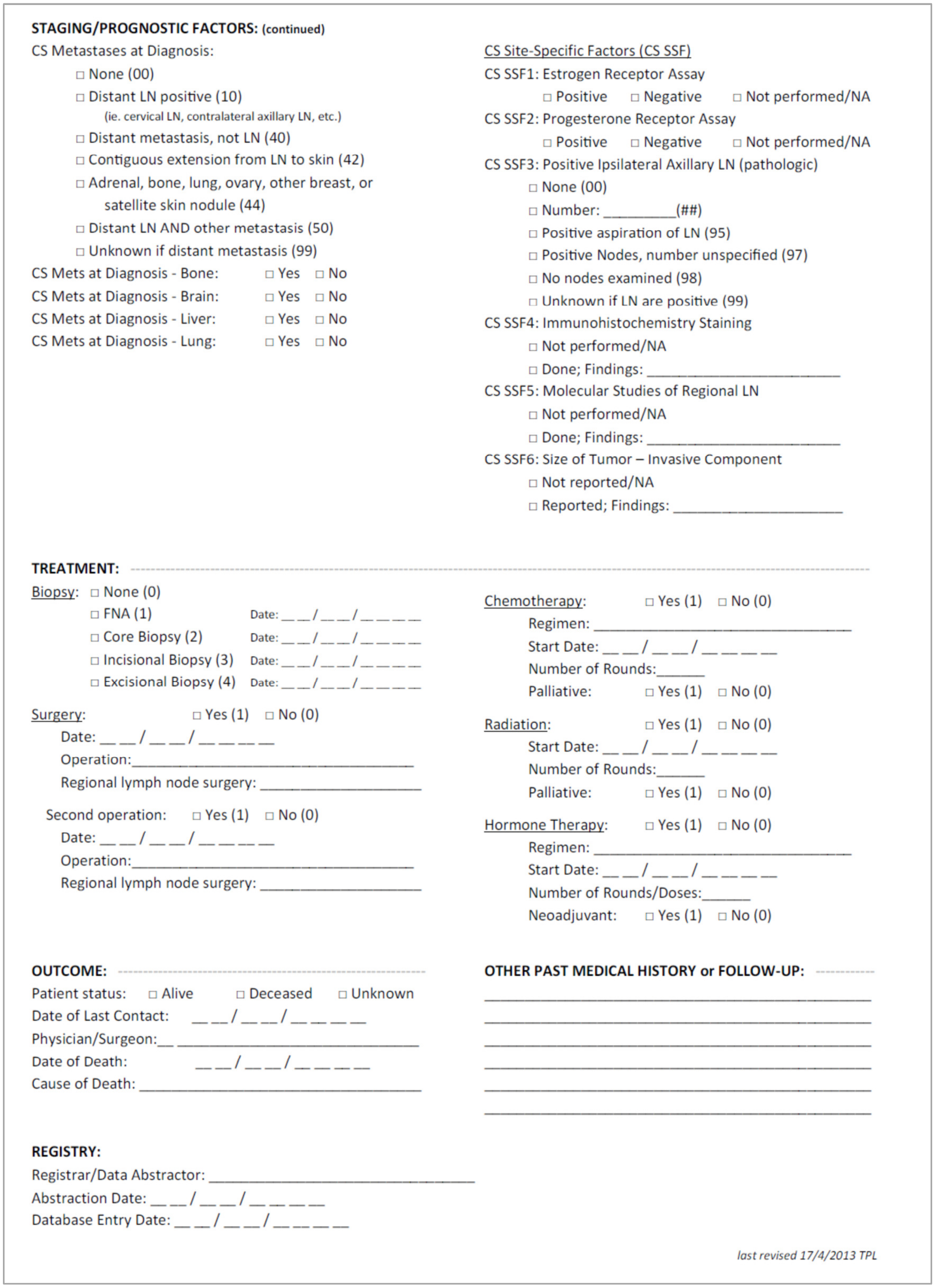
Figure 6. Data Abstraction Form Developed and Utilized in this Ethiopian Breast Cancer Registry



STAGING/PROGNOSTIC FACTORS: **(continued)**

CS Metastases at Diagnosis:
- ☐ None (00)
- ☐ Distant LN positive (10)
  (ie. cervical LN, contralateral axillary LN, etc.)
- ☐ Distant metastasis, not LN (40)
- ☐ Contiguous extension from LN to skin (42)
- ☐ Adrenal, bone, lung, ovary, other breast, or satellite skin nodule (44)
- ☐ Distant LN AND other metastasis (50)
- ☐ Unknown if distant metastasis (99)

CS Mets at Diagnosis - Bone: ☐ Yes ☐ No
CS Mets at Diagnosis - Brain: ☐ Yes ☐ No
CS Mets at Diagnosis - Liver: ☐ Yes ☐ No
CS Mets at Diagnosis - Lung: ☐ Yes ☐ No

CS Site-Specific Factors (CS SSF)

CS SSF1: Estrogen Receptor Assay
☐ Positive ☐ Negative ☐ Not performed/NA

CS SSF2: Progesterone Receptor Assay
☐ Positive ☐ Negative ☐ Not performed/NA

CS SSF3: Positive Ipsilateral Axillary LN (pathologic)
- ☐ None (00)
- ☐ Number: _________(##)
- ☐ Positive aspiration of LN (95)
- ☐ Positive Nodes, number unspecified (97)
- ☐ No nodes examined (98)
- ☐ Unknown if LN are positive (99)

CS SSF4: Immunohistochemistry Staining
- ☐ Not performed/NA
- ☐ Done; Findings: ________________________

CS SSF5: Molecular Studies of Regional LN
- ☐ Not performed/NA
- ☐ Done; Findings: ________________________

CS SSF6: Size of Tumor – Invasive Component
- ☐ Not reported/NA
- ☐ Reported; Findings: _____________________

TREATMENT:

Biopsy:
- ☐ None (0)
- ☐ FNA (1) Date: __ __/__ __/__ __ __ __
- ☐ Core Biopsy (2) Date: __ __/__ __/__ __ __ __
- ☐ Incisional Biopsy (3) Date: __ __/__ __/__ __ __ __
- ☐ Excisional Biopsy (4) Date: __ __/__ __/__ __ __ __

Surgery: ☐ Yes (1) ☐ No (0)
Date: __ __/__ __/__ __ __ __
Operation:___________________________________
Regional lymph node surgery: ____________________

Second operation: ☐ Yes (1) ☐ No (0)
Date: __ __/__ __/__ __ __ __
Operation:___________________________________
Regional lymph node surgery: ____________________

Chemotherapy: ☐ Yes (1) ☐ No (0)
Regimen: _________________________________
Start Date: __ __/__ __/__ __ __ __
Number of Rounds:______
Palliative: ☐ Yes (1) ☐ No (0)

Radiation: ☐ Yes (1) ☐ No (0)
Start Date: __ __/__ __/__ __ __ __
Number of Rounds:______
Palliative: ☐ Yes (1) ☐ No (0)

Hormone Therapy: ☐ Yes (1) ☐ No (0)
Regimen: _________________________________
Start Date: __ __/__ __/__ __ __ __
Number of Rounds/Doses:______
Neoadjuvant: ☐ Yes (1) ☐ No (0)

OUTCOME:

Patient status: ☐ Alive ☐ Deceased ☐ Unknown
Date of Last Contact: __ __/__ __/__ __ __ __
Physician/Surgeon:__ ______________________________
Date of Death: __ __/__ __/__ __ __ __
Cause of Death: ___________________________________

OTHER PAST MEDICAL HISTORY or FOLLOW-UP:

____
____
____
____
____
____

REGISTRY:

Registrar/Data Abstractor: ______________________________
Abstraction Date: __ __/__ __/__ __ __ __
Database Entry Date: __ __/__ __/__ __ __ __

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Figure 6. Data Abstraction Form Developed and Utilized in this Ethiopian Breast Cancer Registry (continued)