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THE PREVALENCE OF BREAST CANCER IN AFRICA AND ESTABLISHMENT OF THE LIBYAN BREAST CANCER REGISTRY

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List of Abbreviations and Acronyms:

- ALND = Axillary Lymph Node Dissection
- BI-RADS = Breast Imaging Reporting and Data System
- BMI = Body Mass Index.
- BRCA 1/2 = Breast Cancer Gene 1 and Breast Cancer Gene 2
- BCS = Breast Conserving Surgery
- C50 = Breast cancer code ICD
- CBE= Clinical Breast Examination
- BSE = Breast Self-Examination
- cm = Centimeter
- CT scan = Computed Tomography
- C = Cytology diagnosis based on microscopic examination of cells
- DCIS = Ductal Carcinoma In Situ
- ER = Estrogen Receptor
- FNA= Fine Needle Aspiration
- G = Gravida (total number of confirmed pregnancies regardless of the outcome of the pregnancy)
- HRT = Hormonal Replacement Therapy
- HER2 = Human Epidermal Growth Receptor 2
- ICD = International Classification of Diseases
- ILC = Invasive Lobular Carcinoma
- IDC = Invasive Ductal Carcinoma
- In Situ = Cancer cells not progressed through the basement membrane
- Kg = Kilogram
- LBCR = Libyan Breast Cancer Registry
- LBCRF = Libyan Breast Cancer Registry Form
- LCIS = Lobular Carcinoma In Situ
- LN = Lymph Nodes
- MRI = Magnetic Resonance Imaging
- mm = millimeters
- mmHg = millimeter mercury
- -ve = Negative
- P = Parity (number of pregnancies a woman has given birth to alive or lost, fetus more than 20 more than weeks)
- PET scan = Positron Emission Tomography
- PR = Progesterone Receptor
- +ve = Positive
- RSA = Republic of South Africa
- SLN = Sentinel Lymph Nodes
- SLNB = Sentinel Lymph Node Biopsy
- TNM / T=Extent of the tumor, N=Regional lymph node metastasis, M=Distant metastasis
- U/S = Ultrasound
- X-ray = Radiological diagnosis based on x-ray scan

THE PREVALENCE OF BREAST CANCER IN AFRICA AND ESTABLISHMENT OF THE LIBYAN BREAST CANCER REGISTRY

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Abstract:

Breast cancer is well-known globally and remains one of the principal health concerns affecting women, and a rare malignancy in men. Although, there has been significant progress made in prevention strategies such as early detection and better treatment in most developed countries, incidence and mortality rates of breast cancer continued to rise. The rise is significant in Africa, a continent low in resources with a growing and ageing population exposed to risk factors leading to developing the disease. Although the incidence of breast cancer is lower in Africa than in high-income countries, mortality rates are high, mainly in women less than fifty years of age.

Like most African countries, Libya is least prepared to cope with breast cancer and cancer in general. Additionally, many Libyans are adopting unhealthy lifestyles together which, together with environmental changes and high life expectancy, is perhaps the cause of rising cancer rates. However, no systematic collection of breast cancer incidence is currently undertaken, which in turn, impacts the implementation of detection and treatment measures.

This thesis sought to evaluate the situation of breast cancer in Africa and specifically, for Libyan patients, through a systematic review of prevalence studies in Africa and by designing a registry for Libyan breast cancer patients.

Objectives :

- To conduct a systematic review and literature-based meta-analysis to provide an evidence-based estimate of the prevalence rate of breast cancer in Africa. This systematic review provides epidemiological data to guide health practitioners, educators and researchers for further studies needed in the field of breast cancer, specific for African patients.

- To design a breast cancer registry for Libyan breast cancer patients. Developing a Libyan breast cancer registry provides an opportunity to learn more about disease development, and the changes through the course of the patient's life. Secondly, we will be able to track the incidence, mortality, and survival of patients diagnosed with breast cancer and their distribution in Libya. Finally, the information will be translated into numbers to aid policymakers in measuring the extent of the problem and help researchers in taking action needed to reduce the breast cancer load in Libya.

Methods:

- A systematic literature search was performed to identify studies retrieved from electronic databases, grey literature and reference lists, with no time and language limits. We have reviewed the available studies addressing the prevalence rate of breast cancer for African patients living in Africa who developed the disease.

- Secondly, the Libyan Breast Cancer Registry (LBCR) is a prospective, hospital-based registry planned to document clinical and imaging characteristics of patients at presentation. Through follow-up, we will document disease progression and treatment practices to reliably determine the incidence of all-cause mortality and worsening disease requiring hospitalization.

Results:

- The overall prevalence rate of breast cancer in Africa was 0.30 [95% CI, 0.26 to 0.34] (22 studies, n=10,795). The prevalence rate of breast cancer for African females was 0.49 [95% CI, 0.38 to 0.62]. South African region had the highest breast cancer prevalence rate, 0.65 [95% CI, 0.24 to 1.26], while the lowest rates of breast cancer were from Central African regions. The use of mammography yielded higher rates of detection, (0.63 [95% CI, 0.46 to 0.82]), in comparison with clinical breast examination (0.31 [95% CI, 0.22 to 0.42]).

- The proposed LBCR comprises parts I, II, AND III.

  Part I consists of demographic data and cancer information detailing personal data such as medical history, general examination, breast examination, methods and results of the diagnosis, and the treatment offered.

  Part II comprises the forms used for continuous follow-up – a new form is completed at each visit. All new information regarding patients' details, new complaints, and investigation findings and any changes or treatment offered at the visit, are recorded in this section.

  Part III documents mortality information. Details are recorded accompanied with a copy of the death certificate, and an autopsy report in case it was required.

The LBCR pack includes consent forms in both English and Arabic languages. Also, it is accompanied by a manual of operation with given answered examples. Furthermore, the form is provided with contact details in case of any required information or explanation needed in the future.

Conclusion:

The clinical picture of breast cancer in Africa differs from Western countries due to the high proportion of patients developing the disease at a younger age and seeking management care at an advanced stage. Currently, there exists no specific breast cancer registry designed specifically for any African patients living in Africa.

The LBCR will provide comprehensive, contemporary data on patients with breast cancer through establishing a baseline figure of the current situation for future local and national comparisons. The LBCR includes ready and accessible information for the temporary and future use of medical elements and researchers in this field and will help in the development of strategies to prevent and manage breast cancer and its complications.

CHAPTER ONE

INTRODUCTION TO MY THESIS:

Breast cancer is defined as uncontrolled growth and division of mutated breast cells. Depending on the site of breast tissue and cell characteristics the cancer is classified and staged. It is the most diagnosed cancer of female around the world and the second leading cause of death.

The primary intent of my thesis was to determine the prevalence of breast cancer in Africa by reviewing the available, best evidence of new and existing data of breast cancer from both published and non-published studies. These results are for assessing the burden of breast cancer on our continent by raising these figures to policy makers to overcome this enormous dilemma; we can also compare our results with other settings in an attempt to follow the changes over time. Secondly, I also created a breast cancer registry specific for breast cancer patients in Libya in the attempt to easily collect information by fellow researchers and medical staff. I focus on the required details related to breast cancer risk factors that are responsible in initiating the cancer, methods of diagnosis that are cost-effective and available, types of treatment that suite the state and conditions of Libyan patients. Beyond that, this registry can be used for patients admitted at any medical center and can provide hospitals, clinics and institutions requirements with costs and staff needed to accommodate patients with breast cancer. This collected information will be translated into numbers to aid policymakers in assessing the extent of the problem and help in taking action needed to minimize breast cancer burden in Libya.

My literature review consists of reviewing the history of breast cancer and selecting the important milestones that lead to the evolution in the field of medicine regarding breast cancer. Furthermore, I have reviewed breast cancer epidemiology and pointed out the latest information

that are available regarding this field. Lastly, I have pointed out the main reasons of the growing burden in Africa.

For this thesis, I have registered the systematic review with PROSPRO. I have followed the recommended systematic review method. My intention is to publish the results with a title of Prevalence of breast cancer in Africa.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

Breast cancer remains one of the principal health concerns that is recognized globally, and although it affects both sexes, breast cancer in males accounts for less than 1% of all breast cancers (1-4).

At the moment breast cancer is the most diagnosed cancer in women, around 2.1 million new incident cases and 626,679 deaths in 2018 for both sexes (1,5). Breast cancer requires significant attention in the less developed regions of the world, particularly Africa because of the lack of infrastructure and resources to diagnose early and to treat individuals effectively (6,7).

The focus of this review is to provide information about breast cancer to clinical health care workers who may deal with individuals with breast cancer in Africa.

2.2 Breast Cancer Milestones

The first documented breast cancer cases are believed to go back to 3000 BCE, based on medical texts written in Hieratic on a sheet of papyrus found in one of the ancient Egyptian tombs (8-10). In 400 BCE, Hippocrates described breast cancer as a humoral disease, implying a disorder in the body fluids (11), while Galen in 200 CE mentioned there were different types of breast tumors, some more dangerous than others. Galen suggested given medication such as opium, castor oil, licorice, sulfur, and salves to cure wounds (12,13).

In the 10th century texts written by the physicians Rhazi and Ibn Sina mentioned that early diagnosis of cancer improved outcomes and that cancer can be managed by removing the tumor tissue in the early stages. However, they also stated that nothing be done in more advanced cases and that the patient is offered only palliative care. Rhazi correlated breast cancer with menstrual bleeding and stated the disease was prevalent in post-menopausal women which agrees with present knowledge (14-18).

Much progress in the diagnosis and treatment of breast cancer occurred in the 19th century (19). William Halsted 1882 carried out the first radical mastectomy - the surgeon removed the total breast with

underlying muscle and ribs in one session. This type of operation was the standard treatment for breast cancer. However, this type of operation is no longer used, and other less radical options are more available combined with chemo-radiotherapy. Breast conserving operations were suggested in 1937, together with radiotherapy as part of the non-disfiguring operation in the management of breast cancer (20-22). By the year 1985 surgeons started routinely removing only the tumor from the breast in patients diagnosed with early breast cancer, followed by radiation therapy (23,24). They found this method was as effective as mastectomy in the management of breast cancer patients. Furthermore, in advanced breast cancer patients in 1988, preoperative chemotherapy was administered to shrink breast tumors and to allow for clear margins and perform less invasive surgeries for cancer patients (25). The first mammogram used to detect breast cancer was by Robert Egan, an American radiologist, reported the findings from the live patient, he has detected an abnormal breast lesion which was proved to be cancerous in 1962 (26,27).

Regarding the link between estrogen, HER2 and BRCA in breast cancer, in 1896, George Beatson was the first doctor to perform ovarian removal as part of breast cancer management in women (21,28). In 1951 it was discovered that estrogen drives the growth of breast cancer which opened a new field in the management plan of breast cancer. Thereafter, Elwood Jensen 1967 discovered that the presence of intracellular estrogen receptors benefited patients who have hormonal dependent breast cancer. Consequently, in 1978 Tamoxifen (an anti-estrogen drug) started being used to prevent the recurrence of breast cancer and also to reduce developing breast cancer in high-risk females 1998. In 1984 the oncogene HER2 positive type as an aggressive breast cancer was discovered which correlates with poor prognosis in patients carrying this type. About ten years later the inherited genes BRCA1 and BRCA2 were cloned, showing that mutations in these genes increased the risk of developing breast and ovarian cancer in women who carry these mutated genes (29,30).

Better detection methods of breast cancer in early stages before any symptoms appear and new targeted treatment for breast cancer are currently under development. There are many different types of breast

cancer in patients that have different characteristics - here we will only discuss the most common types together with a brief review of the main approaches used in the management of these cancers.

2.3 Breast cancer subtypes and stages

Breast cancer can present as a variety of types and subtypes and can be categorized based on the level of spread of the disease and the tissue of origin location of the cancer cells. Table 1 below shows the different types of breast cancer and the percentage incidence of the various sub-types. Breast tumors are divided according to their invasion characteristics (31-33).

Table 1: Types of breast cancer and percentage (32,45,46).

In situ carcinoma 15%–30%	Ductal carcinoma in situ	23%
	Lobular carcinoma in situ	7%
Invasive carcinoma 70%–85%	Ductal carcinoma (no special type)	50-79%
	Lobular carcinoma	8-10%
	Tubular/cribriform carcinoma less than	4%
	Mucinous carcinoma	2%
	Medullary carcinoma	2%
	Papillary carcinoma	1%
Other breast cancers	Sarcomas	lee than 1%
	Lymphomas	less than 1%
	Paget's disease	less than 5%

2.3.1.1 Ductal carcinoma In-situ (DCIS)

Ductal carcinoma in-situ are non-invasive mammary tumors which are often a precursor of invasive breast cancer. These tumors are detected by the presence of micro-calcification lesions in screened patients by mammography and represent approximately 25% of newly diagnosed breast cancer cases (34). Management of ductal carcinoma in situ includes surgery, radiation therapy, and endocrine therapy. Conservative breast surgery is performed in patients with microscopic foci of low-grade DCIS, however, even with an extensive free margin, radiotherapy, post-primary tumor resection is recommended. Sentinel lymph node biopsy (SLNB) is not regularly examined in patients with DCIS, but in patients who have had a mastectomy for the primary tumor treatment, lymph node examination is performed (35,36). Tamoxifen is given for five years in premenopausal women with receptor-positive tumors, while aromatase inhibitors are recommended for the postmenopausal period. Although endocrine therapy is given to DCIS to reduce recurrence rates, no data regarding the improvement of the survival rate has been recorded (37-39).
The prognosis for patients with DCIS is excellent with full excision of the tumor, followed by adjuvant endocrine therapy (40). Figure 1 illustrates the different of presence of DCIS in which the tumor did not cross the duct, while if the tumor crossed the wall of the duct in this case is called invasive breast cancer and the management will be different according to patients' workup.

Figure 1 Showing the difference between DCIS and IDC.

2.3.1.2 Lobular carcinoma In-situ (LCIS)

Lobular carcinoma in-situ is noninvasive tumors that originate from the lobules of the breast. However, they have a high risk of developing into invasive breast cancer. The LCIS are uncommon tumors found when performing a breast biopsy for reasons other than breast cancer in women between the ages of 44 and 46 years during premenopausal. However, management depends mainly on the histology of the cells. In pleomorphic LCIS (identified on an excision biopsy), evaluation of the surgical margins may indicate the need for re-excision. If an invasive carcinoma is detected, the appropriate management should be initiated accordingly (41-44).

2.3.1.3 Paget's disease

Paget's disease is a rare form of breast cancer usually less than 5% of all breast cancers that begins in the ducts and spreads to the skin of the nipple and areola. Patients usually present with crusts, redness, or oozing from the nipple. The prognosis is better when no lump is involved, and the tumor involving only the skin. Treatment consists of removal of the lump by breast-conserving surgery followed by radiation therapy, and the prognosis in this stage is excellent. In contrast, if the biopsy reveals invasive ductal cancer, staging is required followed by appropriate treatment (45,46).

2.3.1.4 Infiltrating ductal carcinoma (IDC)

Infiltrating ductal carcinoma is the most common type of invasive breast cancer and accounts for 50-75% percent of invasive breast lesions. IDC arises from the cells lining the milk duct, and the cancer cells gradually invade the duct wall into surrounding breast tissue and spread to other parts of the body (figure 1). This type of breast cancer is frequently diagnosed at an early stage in regions were mass screening modalities are performed. They appear as numerous clusters, and pleomorphic calcifications, high-dense masses with calcifications, or irregular speculated border by mammogram examinations. In late-stage,

women present with a palpable painless fixed mass with skin changes and palpable lymph nodes. The treatment plan is given based on the hormone receptor status and stage (43).

2.3.1.5 Infiltrating lobular carcinoma (ILC)

Infiltrating lobular carcinoma is the second most common type of invasive breast cancers, accounting for about 6 % of invasive lesions. They differ from infiltrating ductal carcinoma by having a higher frequency of bilateral breast involvement and lesions are usually multi-centric. They usually affect older women and are usually estrogen receptor positive. Infiltrating lobular carcinoma tends to metastasize later than invasive ductal carcinomas. Moreover, the cancer cells migrate to unusual locations such as the peritoneum, meninges, and gastrointestinal tract (32,42,47,48).

2.3.1.6 Other histologic types of breast cancer: They account for less than 5% of all invasive breast cancers. They include metaplastic, mucinous, tubular, medullary, adenoid cystic carcinoma, and papillary carcinomas (49-54).

2.3.1.7 Breast sarcoma

They are rare primary malignant tumors of the breast arising from connective tissue and accounting for less than 1% of primary breast cancers. Sarcomas are treated by surgical removal of the tumor, and radiation therapy also can be added. Because this type of cancer does not spread by the lymphatic system, lymph node dissection is not required (55,56).

2.3.1.8 Breast lymphoma

They usually present as a painless breast mass, a distinct subtype of Non-Hodgkin lymphoma, and treated with chemotherapy (57).

2.3.2 Breast tumor stages

The TNM system is internationally accepted used to determine the disease stage based on tumor size (T), whether or not lymph nodes involved by the tumor (N) and has the cancer cells metastasized to other parts of the body (M). The TNM system is classified from 0 to IV and accordingly, the treatment is offered to patients (58). However, the management plan will consider patients' status, tumor characteristics, HER2, and hormonal receptor type before the start of treatment. Stage 0 is a pre-cancer stage were tumors do not cross the wall of ducts or lobules, this stage is usually found in the regular screening of high-risk patients or as routine mammography checkups, like stage I the treatment of breast cancer patients is very effective. While in stages II and III of breast cancer, the tumors cells have moved beyond the basement membrane of ducts or lobules and the surrounded tissue with the involvement of regional lymph nodes. Stage IV, on the other hand, involves extension of tumor to other regions of the body, this stage is incurable, however, with current advances in medical technology, excellent care, and support, as well as personal motivation, more women are living longer (58).

The incidence rates of breast cancer appear to have increased in previous low incidence places and knowledge is still limited about how geographic variations in breast cancer rates relate to specific etiologic factors (1,2).

2.4 Global Burden

Breast cancer is the most frequent cancer recognized in women around the world. The latest estimate by GLOBOCAN in 2018 has shown that there are more than 2 million new cases diagnosed with breast cancer (accounting for 11.6% of all new cancer cases) and unfortunately, it has caused more than a half-million deaths (6.6% of all cancer deaths) in the same year (1). Figure 2 below shows the difference between new cancer cases and number of cancer-related deaths of both sexes in 2018.

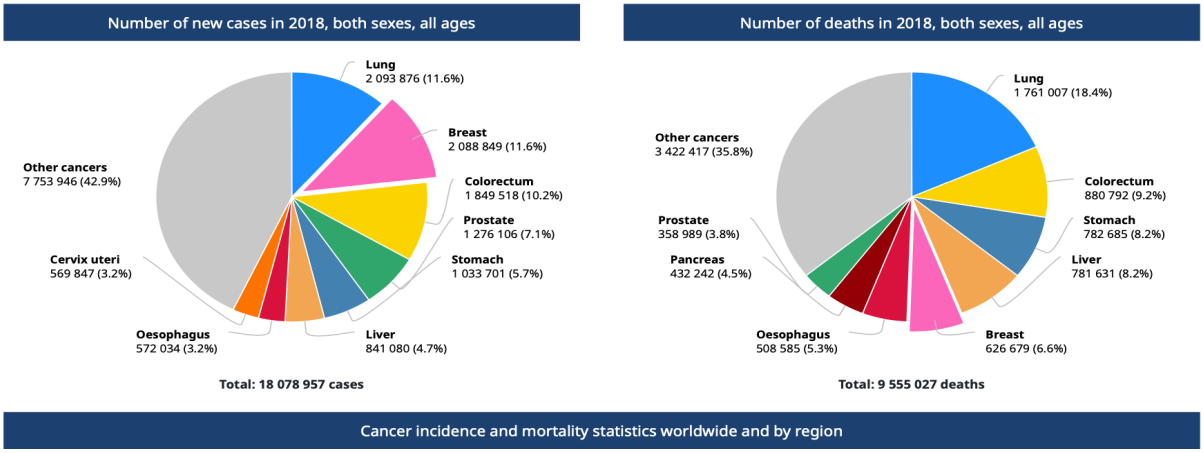

Figure 2 Breast cancer incidence and mortality compared to total cancer GLOBOCAN (1).

The highest incidence rates of breast cancer are recorded from Australia/New Zealand, Northern, and Western Europe, Belgium. The presence of related risk factors and the availability of massive screening by mammograms may reflect on the high incidence rate of this disease in these regions (1,6,7,59). As a result of increasing population size and aging of the population and an increase in exposure to cancer risk factors, breast cancer incidence is rising rapidly in previously lower-risk areas, such as in South America, Africa, and Asia (1).

The incidence and mortality statistics of breast cancer shown in figure 3 presents a very interesting picture. Despite the high incidence rates of breast cancer in Australia and New Zealand (ASR, 94.2 per 100 000); Western Europe (92.6); Northern Europe (90.1); Northern America (84.8); and Southern Europe (80.3), the breast cancer mortality rates for these countries (quoted as ASR per 100 000) is similar if not lower than other countries with much lower incidence rates of the disease (12-15) in high incidence countries vs 25 in Melanesia and 18 in Northern Africa). In low income countries with high incidence rates, women usually present in the later stage at diagnosis because screening approaches are poor combined with limited treatment options, resulting in lower survival rates. In terms of mortality rate Melanesia, Fuji had the highest record in the world see Figure 3. Mortality rates are reflected by the

occurrence of breast cancer as well as the availability of early detection of asymptomatic lesions and access to effective treatment (1,59).

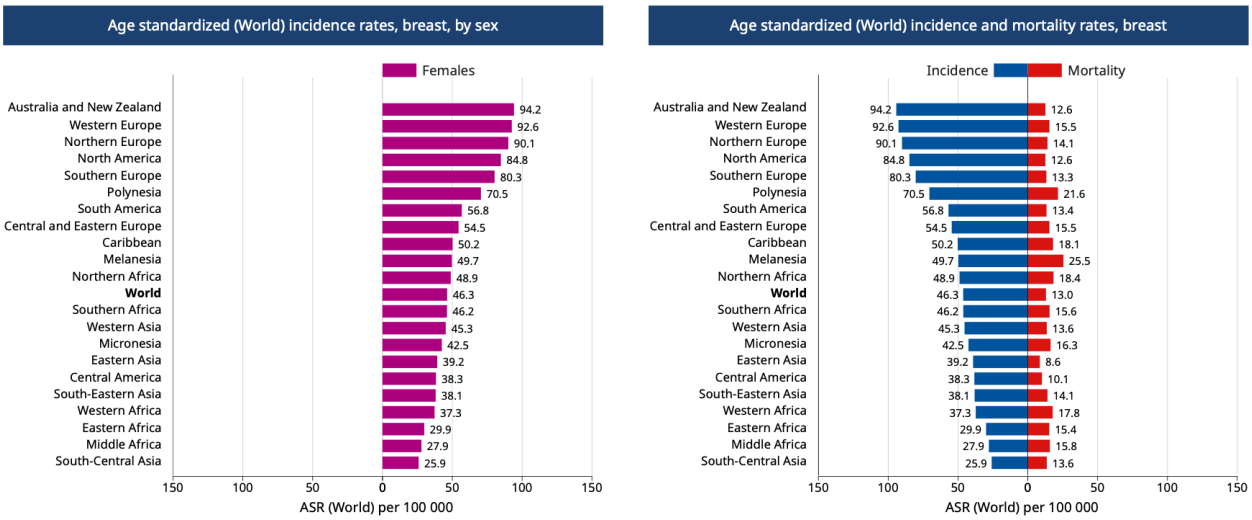

Figure 3 lists of the both incidence and mortality rate by countries GLOBOCAN (1).

2.4.1 Breast cancer burden: Africa

Considering the information presented in the previous section, it should be clear that despite the low incidence of breast cancer in most African countries, the mortality rate is similar; if not moderately higher than in those countries with high incidence (Figure 3). This could be that the majority of women show up late with advanced disease, delay in referrals to specialty centers, the high cost of drugs, cultural barriers, and unavailable infrastructural facilities due to unstable governments which remain a common circulating topic (60).

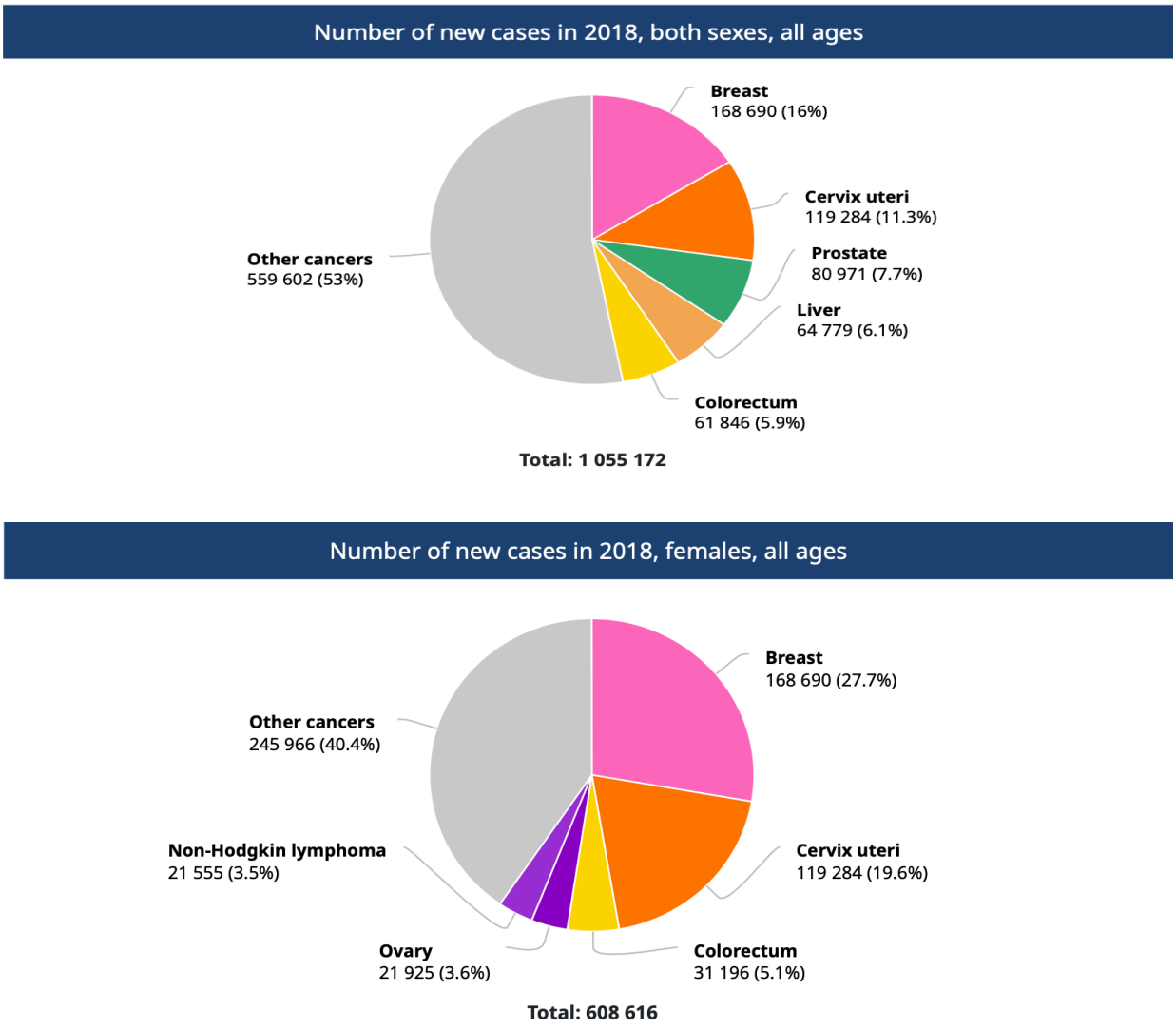

Figure 4 Number of new cases of breast cancer in Africa in both sexes and for females specifically GLOBOCAN (1).

Incidence data in low and middle-income countries are calculated either from regional incidence data from large cities or the data is collected from neighboring countries. In Africa, only 1% of its population is covered with high-quality registries (61,62). That means that many people that develop cancer are not identified impacting on the ability to plan and supply the health service, therefore, leading to increasing cancer burden in Africa. Urgent activation and functioning of high-quality population-based cancer

registries to provide evidence-based cancer control programs are required (63). At the moment, only a few have been selected to submit their data of cancer incidence, because the others provide poor data quality. Currently, eight countries, Algeria, Egypt, Libya, Tunisia, Malawi, South Africa, Uganda, and Zimbabwe, report an annual incidence data. However, only four of the African countries supply mortality statistics from the total of 54 countries (64-67).

In the year 2018, a total of 168 690 new cases was diagnosed with breast cancer representing 27.7% of the total cancer cases diagnosed in African women. (Figure 4). There was a moderate variation in estimated breast cancer incidence rates across the African regions. The estimate of age-standardized incidence rate per 100,000 women per year were (27.9) in Middle Africa, (29.9) Eastern Africa, (37,3) Western Africa, (46.2) Southern Africa, and (48.9) in Northern Africa. The rate was lowest in Middle Africa and highest in the Northern region of the continent, which could be explained by elevated exposure to risk factors, increased awareness campaigns and the commencement of screening modalities in certain parts of Africa (62,68-70).

2.4.2 Breast cancer burden: North Africa

The Northern African region is separated from Europe by the Mediterranean Sea in the north, and the Saharan desert from the rest of Sub-Saharan regions Africa. They include a total of seven countries (Algeria, Egypt, Libya, Morocco, Sudan, Tunisia, and Western Sahara) with an estimate of 245,926,250 people living in the year 2020 and share a same ethnic, cultural and linguistic identity (71). The majority of the population is a mixture of migratory Roman, Greek, Arabs, and Europeans distributed across the North region over time integrated with indigenous natives gives them unique features from the rest of Africa (72).

In terms of health care, North Africa faces several challenges, including a weak system, lack of funds, and poor infrastructure. However, because of a prompt rise in cancer patients in these countries, professional interest has grown towards the disease recently (6,7,73).

Breast Cancer in North Africa

Breast cancer is by far the most common tumor affecting women in North Africa, and estimated incidence from population-based registries was 29.3 per 100 000 person-years (73). However, despite its lower incidence in comparison with western countries, the mortality rates are higher in most of the African regions (1,73,74). Also, the incidence of male breast cancer in North Africa is the same as in the Western parts of the world. However, the relation to female breast cancer is higher, it could be explained by the low incidence of female breast cancer in comparison to Western countries (1,74). Furthermore, in the Northern African region breast cancer noted the presence of more aggressive types such as inflammatory breast cancer, however, the underline cause not been explanation (74).

Prevalence of breast cancer risk factors in North Africa

Hospital and laboratory-based data reported the predominant hormonal model is the major related cause of breast cancer which is similar to studies from developed countries (73-81). However, risk factors such as the age of women having a first child, the number of children a woman conceives, usage of hormonal drugs, and the duration of breastfeeding have changed recently and becoming more towards less protective from breast cancer in the developing regions (74,78-87). Women from the Arab nation are changing their habits using hormonal therapy in controlling the number of births, late marriage, and having their first child at an older age. Furthermore, more alcohol consumption, reduced in a healthy diet, and lack of physical exercise all could explain the increase in the incidence of breast cancer in North Africa. Although the behavior of women has changed, no clinical trials performed in reducing the risk of breast cancer in Northern African women (74-87,88).

Genetic studies and family history risk assessment are limited and restricted to breast cancer patients having a BRCA1 or BRCA2 mutation in Algeria, Tunisia, Egypt, and Morocco unlike, in Europe and the USA (74,78,79). While in the rest of the countries, no genetic studies were published (74,82). Trials in the management of breast cancer do not exist and the only available ones are part of screening or awareness of the disease (90,91). However, data from population-based registries from the North African countries are more prominent in providing updated information from its population in comparison with other African countries (1,74,92). In fact, most reliable high- quality data are from most of the North African countries have been selected to submit their data with the International Agency for Research Cancer (IARC) (92,93).

Screening of breast cancer in Northern Africa

The majority of African countries' screening programs for breast cancer are not activated (93). However, a few promising initiatives have emerged in the last years. Although these programs included screening a small number of women, resulted in a noticeable increase in early mammography-detected cancers (74,93-102). Women aged 40 years and above were screened by mammograms in Egypt, Tunisia, and Morocco, however, the small number of women attended could be explained by lacking awareness campaign or fear of detecting cancer (90,99). On the other hand, screening women younger than 40 years was performed by clinical breast examination in both Egypt and Sudan indicated that breast cancer prevalence was high in young age groups (90,91). Despite the initiation of screening programs, there is still a controversy regarding the cost-effectiveness of screening in these regions (74,82,90,96,103,104).

2.4.3 Breast cancer burden: Libya

Libya is one of the largest North African countries and only 6,868,460 million citizens living in 2020. Although, being one of the wealthiest countries, yet the country has a serious ongoing problem. One of its chronic problems is mismanagement, corruption, and insufficient health care system. In the last years, the

Libyan health professional is facing new challenges, communicable diseases are returning, increasing non-communicable diseases, and war wounds have left the health system near collapse (105.106).

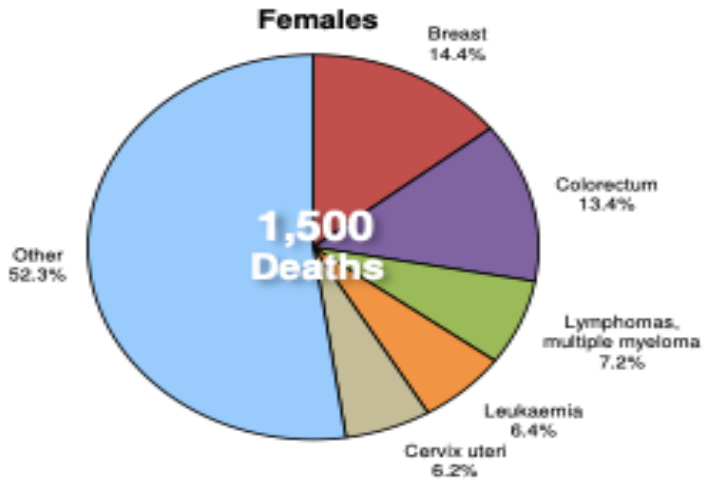

Figure 5. World Health Organization - Cancer Country Profiles, 2014.

Although the Libyan government offers free healthcare to its population cancer remains a low priority, resulting in high mortality rates in both sexes (105,107-109). In women, the most commonly diagnosed cancer is mammary carcinoma and its incidence is 23.8% for all female ages and has caused 14.4% female cancer mortality seen in figure 5 (105-110). The large number of women dying in Libya from breast cancer could be because of late diagnosis and unavailable management plans (74,104,111-116). Also, risk factors like most of the North African women Libyan women marry late and have their first child at a late age. Nowadays, Libyan woman has fewer children than in the past, the fertility rates was calculated 2.24% in the year 2018 almost half of what was in 1990 (117). Adding the duration of breastfeeding has changed recently, women tend not to breastfeed and use artificial milk to nourish their babies (118-121). Another related risk factor in developing breast cancer lack of physical exercise, it is estimated that 42.3% of females do not exercise and around 38 % of the Libyan females are obese, which

could explain the rise in the incidence of breast cancer (118-125). Furthermore, consuming an unhealthy diet high in fats and low in fibers, fruit, and vegetables could also increase the risk of developing the disease (122). This change in lifestyle together with environmental changes, hormonal changes, and high life expectancy is perhaps the cause of rising cancer burden in Libya (74,103,104,111).

Breast cancer is more prevalent in younger age groups with a median age of 44 years, mainly during the pre-menopause period around ten years younger than in high-income countries and similar to most of the African region (78,107-110). In contrast, the median age group in males is 61 years; men pursue medical facilities only in an advanced stage that could explain fewer survival rates than females. The overall five-year survival rates are 57% for men compared to females 78%, which is more than most parts of Sub-Saharan Africa and almost similar to the rest of the North African region (74,81,88,107-112,113).

Many reasons delay patients' presentation for cancer diagnosis, or the start of treatment, including such as socioeconomic factors, unaware of a less common type of symptoms related to breast cancer which, could be because of lacking awareness programs (108,112-116). Another reason could explain late-stage presentation women having tried traditional herbal and spiritual treatments first before attending cancer centers (74,82,88,93). Furthermore, Libya is considered one of conservative religious countries and women who develop breast cancer think its destiny due to their firm belief resulting in not attending any check-ups or complain about their problems (74,82,88,93). Also, fear of the disease treatment will leave their body disfigured and feeling ashamed from family members and spouses could explain the hesitation in early attending medical advice (74,82,88,106,111,116). Therefore, women will only seek advice from medical services at a very late stage. By this time, cancer may have already metastasized to the lymph nodes and then spread to the other parts of the body. Thus, the option of treatment will be severely limited to patients at this stage, and the patient exposed to more medication toxins to the body which, enhances

damage to the major organs and leads to an early death. Other reasons related to health care provider–mediated factors delayed referrals, delays in obtaining diagnostic confirmation, and availability of medications can prolong in the time of women starting breast cancer management (74,104,105,116,110). Furthermore, the health staff formed by both local and non-local members when leaving causes shortage, together with lacking training of local persons in all health sectors, are all part of the enormous struggles facing Libya today (105).

Management of breast cancer in Libya

Primary cancer prevention programs such as tobacco control, alcohol control, obesity prevention, and promotion physical activity are minimal to non-existent for non-communicable diseases (105-117,126). Screening and early detection are widely recognized as being a principal factor in reducing the mortality from breast cancer (6,7). However, awareness programs, mass screening methods are not implemented for breast cancer even though there are around 12 mammogram machines available and the majority of the laboratory can offer diagnostic tests (126). As a result, Libyan patients gave up on the collapsed system, patients seek medical advice from neighboring countries or even travel far too western regions (105,106).

Breast cancer management is composed of a multidisciplinary team that involves different specialties: breast surgeon, medical oncologist, radiation oncologist, pathologist, psychologist, anesthesiologists, and health educator at the Oncology centers/units (125-128). The full team usually available and meet to discuss their patient's management plan. However, young women in Libya do not undergo breast-conserving surgery because of the low number of radiation therapy machines and availability of radiologist are only in the major cities (125-128). There are only four radiology machines and seven radiologists covering all cancer patients around Libya (126). Also, cancer medication is usually not available and costly leading to losing trust in the Libyan health system (105,106).

Furthermore, unfortunately, genetic work, follow-up patients, and trials regarding breast cancer in Libya has not been done, although the majority of research based on hospital records have shown an increase in the incidence of cancer patients. However, population-based registries have emerged recently, and a few studies became available (73,74). In 2002 the first population-based cancer registry published its data from Benghazi Medical Center revealed that the most common cancer among Libyan females was breast cancer (73,74.107). Yet, these results were only covering 28% of the total population. (107). The most commonly diagnosed type of breast cancer in Libyan females was invasive ductal carcinoma and higher tumor grade was the predominant type of all cases (107,125,127). One explanation for the grade differences may involve the more active proliferation in the premenopausal of Libyan female breast cancer, which is similar in young African women diagnosed with breast cancer (74,125). Most Libyan breast cancer women had involved regional lymph nodes at the time of surgical removal of the primary tumor mass and approximately more than half of Libyan patients were classified in stages III and IV (109,113,127,128).

Cancer expected to increase across Africa, including in Libya, preventive measures associated with lifestyle risk factors, and implant early detection methods suitable for Libyan's can overcome the cancer burden.

The increase in breast cancer incidence around the world is probably associated with Westernized lifestyles, unhealthy diet, alcohol use, and sedentary lifestyle alongside changes in reproductive patterns causing higher risk in developing the disease (1,59-62).

2.5 Risk factors of breast cancer

The risk factors for breast cancer can be divided into two broad categories -hereditary and non-hereditary factors. The majority of breast cancer cases are due to non-hereditary factors, and only a small percentage

of breast cancer cases (5-10%) is directly due to inherited mutations in very specific genes, for example the BRCA gene (129,130).

2.5.1 Nonhereditary factors

Researchers have identified several risk factors; however, it is still not clear why some females do develop the disease and other not (131,132). The leading cause of breast cancer remains unexplained (131,132). Factors which are associated with increased risk of breast cancer include living an unhealthy lifestyle such as being overweight, lack of exercise, eating an unhealthy diet, and drinking alcohol (132-136).

The more we age, the more opportunity for genetic damage in body cells, and the body is less capable of repairing abnormal cells. Therefore, age is a common risk factor for developing breast cancer. However, African and African ancestry women develop breast cancer almost ten years younger than women from Western parts of the world. Even though those African women develop cancer at a younger age, they usually present with an aggressive disease type, which requires further investigation (137,138).
Women that have high breast density have a higher risk of developing breast cancer — the density of breast tissue reflected by both the amounts of glandular and connective tissue to adipose tissue. Furthermore, reading mammograms to detect breast lesions is harder in high dense breast tissue than less dense breasts resulting in false-negative reading (139,140).

Caucasian women are slightly more likely to develop breast cancer than African ancestry or African women, but mortality rates are higher in women of African descent. The high incidence in Caucasian women could be explained by increased accessibility to early screening by mammograms and other screening methods in high income setting, but probably also to an increased exposure to environmental risk factors. On the other hand, African women usually seek medical advice at an advanced stage of the

disease because of a lack of awareness and lack of population screening programs resulting in worse outcomes (1,7,141-143).

Overweight women (having a body mass index of more than 25) have a higher risk of developing breast cancer compared to women with a healthy weight, especially after menopause (133,135). The relationship between menopause and the use of hormonal replacement therapy (HRT) and breast cancer depends on the duration of use and type of hormone used. HRT use has a strong association with the development of breast cancer and studies have shown that the incidence of breast cancer decreased in women after eliminating the use of HRT to ease menopausal symptoms (143-145).

One of the reasons women develop breast cancer is that breast tissue ultimately develops and responds to high levels of estrogen hormones, which is produced in lower amounts in men (4,146). Prolonged exposure to hormones that are produced by the ovaries is associated with an increase in breast cancer risk, including early onset of menstruation, and late onset of menopause. Furthermore, exposure to high levels of hormones for extended periods such as conceiving a first child at a late age or never given birth are associated with an increased risk of developing breast cancer. Conversely, pregnancy and breastfeeding reduce a woman's lifetime number of menstrual cycles, lowering the exposure to endogenous hormones, which are associated with a decrease in breast cancer risk. Besides, pregnancy and breastfeeding have direct effects on breast cells, causing them to differentiate, or mature so that they can produce milk, therefore, lowering the risk of developing breast cancer (147-149).

Previous chest exposure to therapeutic ionizing radiation at a younger age, is associated with an increased risk of developing breast cancer, e.g. patients diagnosed with Hodgkin lymphoma (150,151). Survivors of an atomic bomb or nuclear plant accidents have also associated with an increased risk of developing breast cancer (152). Exposure to diagnostic radiation in women with inherited BRCA1/2 (for example,

exposure to diagnostic levels of irradiation such as mammography, chest radiographs, diagnostic spine imaging, and computed tomography scans) have a higher risk of developing breast cancer (153).

Furthermore, some factors may reduce the risk of developing breast cancer including breastfeeding and regular physical activity (135,154-157). A diet rich in fresh fruits, green vegetables, fish, and olive oil may result in lowering the risk of developing breast cancer (136,158-160). Other diets that consist of high concentrations of soybeans (legumes) and lignans found in a variety of fruits, vegetables, and cereal products are still under investigation and the evidence in preventing breast cancer is still pending (161). In contrast, a diet rich in amounts of fats and red meat may be increase the risk of developing breast cancer, although, studies are still ongoing (162).

2.5.2 Hereditary risk factors

A positive family history of more than two young relatives with breast cancer has a severe risk of developing breast cancer at an early age. Specific genetic mutations which predispose to breast cancer are suspected in females less than 50 years with a family history of breast or/and ovarian cancer. However, they only account for 5-10% percent of all breast cancers and include mutations in BRCA1 or BRCA2 mismatch repair genes. BRCA mutations are seen more frequently in Ashkenazi Jews and genetically related communities, particularly if they are affected by breast and ovarian cancer at any age. Also, men diagnosed with breast cancer are suggestive of BRCA mutations (129). All patients suspected of having genetic predisposition should undergo a DNA test for gene sequence analysis (139).

Screening of breast cancer if done at an early stage before symptoms appear will generally achieve a good prognosis for individuals diagnosed with breast cancer (163-165). There are many screening tests available to detect tumors before the development of signs and symptoms.

2.6 Screening for breast cancer

Like any part of the body, the breast consists of many microscopic cells that execute the functions of breast tissue and also divide to form new cells to replace dead cells. However, sometimes, these cells undergo changes which are not detected and start to proliferate rapidly, resulting in tumor cells. Not all abnormal cells are malignant, only the ones that invade surrounding tissues or move to another organ. Therefore, these tumors require detection and treatment to prevent life-threatening problem (45,49).

A variety of screening approaches are described below, recognizing that some will be less available than others depending on the medical infrastructure available in the region, and socio-economic context of the community.

2.6.1 Breast Self-Examination (BSE)

It is recommended that this method is performed by women every month after each menstrual cycle. Women are trained on how to examine the breast regularly, and symptoms and signs are explained when visiting a health care unit and a pamphlet explaining the method is handed to females regularly. Individuals will inspect their breast in front of the mirror, with regular palpation each month. This method is cheap and noninvasive, and the individual will be more aware of her breast and can easily detect any changes that appear, which should be followed by a clinical examination (see further) However, studies have not proved that breast self-examination can reduce mortality (166).

2.6.2 Clinical Breast Examination (CBE)

This method includes a full detailed history taken from the patient when visiting the health professional. The physician will document the patient history and will perform a full inspection and palpation of the

breast and axilla. This method is the oldest in screening for breast cancer. Any abnormalities detected will be examined in detail. The CBE has increased the screening sensitivity of young women with dense breasts, however, effectiveness in reducing mortality from breast cancer has not been tested through randomized clinical trials yet. It remains an integral part of the evaluation of women with breast complaints or abnormalities. In low resource settings with high risk in developing breast cancer at a young age, no studies have been performed to indicate the usefulness of this method. Therefore, they are used as part of the screening methods for breast cancer when mammography is either not available or not recommended for certain age groups (141,166,167).

Likewise, clinical assessment of the axilla is not a reliable method since palpable lymph nodes do not indicate secondaries. For this reason, a histological examination of the removed lymph node is the most accurate method for assessing breast cancer spread (37,168).

2.6.3 Mammography

Mammography is a specific imaging procedure for the breast and axilla that uses a low dose of x-ray. It is a noninvasive test most frequently used in screening purposes, diagnosis, and follow-up of breast cancer. Among all the imaging modalities developed for breast cancer screening, the mammogram is an imaging technique that has been shown to decrease breast cancer-related deaths (169-172). The sensitivity of mammograms in screening is 77-95%, and the specificity is 94-97% (173). The mammography reading uses the Breast Imaging Reporting and Data System (BI-RADS), scored from 0-6 with each scoring indicating risk for further examination in suspected breast lesions (174). Nevertheless, mammography may miss up to 20 percent of underlying breast cancers resulting in false-negative results that increase morbidity and early death, whereas, false-positive readings generates unnecessary biopsies (175).

Detection of cancer by mammography before symptoms and signs are present have shown a reduction of mortality rates by 20 % (172,173). However, mammograms are not used in pregnant or lactating women,

only in emergency cases. Furthermore, mammograms are not sensitive for women with breast implants or who have scar tissue from previous surgical procedures or trauma.

Mammographs are not recommended before the age of 40 years or above 74 years. However, in certain areas around the world, women develop cancer at an earlier age, and mammography is not sensitive in this age group because breast tissue tends to be dense, making mammograms tests less effective. Women 40 -49 years with a first-degree relative are advised to start screening before50 years. However, exposure to repeated by mammography can increase the risk in developing breast cancer, especially in high-risk women with the BRCA mutations who starts screening for breast cancer at an early age (39,176).

2.6.4 Ultrasonography (USG)

Ultrasound uses sound waves to generate an image, and they are more useful in differentiating whether a mass is solid or cystic. However, determining if the abnormality found is cancerous or calcified is not possible. The sonographic malignancy features include; hypo echogenicity, internal calcifications, shadowing, speculated mass, indistinct, or angular margins. Ultrasound is not routinely used for screening purposes, as it has not shown any survival benefit. However, in young suspect patients with dense breast tissue, this approach may detect additional breast lesions (177-179).

2.6.5 Magnetic Resonance Imaging (MRI)

MRI is a tool designed to use radio-frequency waves, a powerful magnet and computer for the diagnoses, staging, and development of treatment plans for diseases like breast cancer. MRI is a high-quality noninvasive technique for breast imaging for better sensitivity and specificity in detecting breast in high-risk women with dense breasts (180). Additionally, in patients with unknown primary tumor, this approach is considered an ideal tool to search for the original tumor. They are also used in the evaluation of the local extension of cancer and can differentiate between surgical scars and local recurrence in

conservative surgery of breast cancer. Furthermore, MRI can be used to evaluate the response to neoadjuvant chemotherapy. Screening with MRI for breast cancer has shown a reduction in morbidity and mortality, due to its high sensitivity in the detection of small tumor clusters. Nevertheless, they cannot detect micro-calcification as effectively as mammography can (181).

They are costly instruments and are unavailable in many centers. However, because MRI's are so effective in detecting lesions, the disadvantage is that they result in more biopsies being requested and increase patient anxiety and cause delays in the initiation of treatment. Therefore, alternative methods, such as ultrasonography are recommended (181.182)

2.6.6 Tomosynthesis

Tomosynthesis is also called three-dimensional mammography or Digital breast tomosynthesis. This is an advanced form of breast imaging that uses low-dose x-ray and computer reconstructions to create three-dimensional images of the breasts. They can generate accurate images and provides precise information in more dense tissue. Therefore, less biopsies are required and is best in the early detection of breast cancer lesions in women with dense breasts. Tomosynthesis has not been recommended as a screening modality since there is insufficient data available to measure the reduction in mortality rates. Although women are exposed to more radiation with this type of tool, there is less requirement for repeated images (183,184).

2.6.7 Positron Emission Tomography (PET scan)

Because cancer cells have a higher metabolic rate than noncancerous cells, cancer cells show up as bright spots on PET scans which image highly metabolically active cells. Therefore, they can help identify areas of cancer that an MRI or CT scan may miss. They are used to monitor the patient after receiving treatment and detect signs of cancer recurrence. However, they are costly tools and not used as a regular modality in detecting breast cancer (185-187).

2.6.8 Computerized Axial Tomography (CT Scan/ CAT)

CT scanning is a procedure based on x-rays that captures information from different angles combined with computers to create images which can be recombined to provide a high revolution view of body parts of interest. They are not routinely used as a screening modality for breast cancer. Depending on the patient's symptoms, CT scans are requested to guide in the assessment of cancer metastasis. However, they have a slightly increased risk of causing cancer and are not used in pregnancy (188).

All types of screening modalities are used in detecting and determining the extent of suspicious breast lesion; however, accurate diagnosis of cancer can only be performed by a histological examination of tissue biopsies.

2.7 Type of Biopsies

Most breast malignancies arise from epithelial elements, most commonly in the terminal ducal lobular unit. However, there are various histologic types of breast carcinomas, which differ both in microscopic appearance and biologic behavior. Consequently, the histological examination of biopsied breast tumor tissue is essential for the diagnosis and development of the subsequent treatment plan for breast cancer. Various biopsy modalities are routinely used to acquire sample tissue for histological analysis.

2.7.1 Fine needle aspiration biopsy (FNA)

The FNA is a procedure performed by using a thin needle to remove a small sample of cells by negative pressure. The cells are then examined and scored from one to five, indicating the range from benign cells to suspected malignant. However, bruising, bleeding, infection, and pain are the main side effects caused

by this procedure. Additionally, FNA has poor diagnostic results compared to core biopsy (they provide the type and characteristics of tumor unlike FNA), and repeated biopsies are common due to small sample sizes acquired. In a poor resource setting, FNA is used to diagnose breast cancer, because it's cheaper and less invasive, but the role in diagnosis is limited to differentiating between benign or highly suspected cells (189.190).

2.7.2 Core needle biopsy

This procedure uses a broader needle to remove a larger sample of tissue under local anesthesia. Core needle biopsies are recommended to diagnose breast cancer. They are the best non-surgical biopsy procedure because they can provide enough tissue to detect cancer type, grade, and receptor characterization of the tumor (190).

2.7.3 Image-guided biopsy

A biopsy performed by guided imaging such as mammography, ultrasound, or MRI when the lesion is identified by imaging and cannot be detected by clinical examination. A stereotactic biopsy is done with mammography to help guide the needle under local anesthesia. A small metal clip is placed where the biopsy sample was collected for additional procedures if the biopsy is positively identified as breast cancer. The titanium clip will not interfere with future imaging tests. The procedure can be done using a fine needle, core biopsy, or vacuum-assisted biopsy depending on the amount of tissue being removed (192-194).

2.7.4 Wire localization biopsy

The wire localization biopsy is another image-guided biopsy used to sample abnormal lesions of the breast. This method is used when the required tissue for examination is too small to be detected by other

approaches. The radiologist inserts a wire at the site of lesion in the patient, and then the patient is shifted to the operation theater to remove the suspected area under general anesthesia (195).

2.7.5 Surgical biopsy

Generally, involves the surgical removal of a large amount of tissue for pathology analysis, however, this approach is not recommended for the diagnosis of breast cancer (196).

2.7.6 Sentinel Lymph Node Biopsy (SLNB)

The SLNB is a procedure used to provide accurate lymph node staging for breast cancer patients. In the negative histological reading of lymph nodes, axillary dissection not required, thus reducing the postoperative side effects of lymphedema and paresthesia observed in breast cancer patients.

The SLNB procedure involves placing a dye or radioactive agents or both in the tumor bed. The dye or radioactivity will appear in affected lymph nodes by dissemination through the lymphatic system. The suspected nodes are removed for examination, and if the SLNB is negative, there is a good chance that all axillary lymph nodes are negative. The sensitivity of SLNB ranges from 90-95% - however, despite the use of this method, there is still a low recurrence rate after surgery. Meanwhile, if the result show more than three lymph nodes involved with cancer, axillary lymph node dissection is undertaken (ALND) together with the removal of the primary lesion (168,197).

2.8 Treatment

All breast cancers patients should be tested for estrogen (ER), progesterone (PR) receptor, and over-expressions of human epidermal growth factor 2 receptors (HER2). The information of the receptor status of the cancer tissue is critical for both prognostic and therapeutic purposes in newly diagnosed breast cancer patients. There are four subgroups of breast cancer based on gene expression profile, treatment and prognosis are given accordingly. Luminal A breast cancer subtype is the most common subtype, and they carry the best prognosis of all breast cancer subtypes (ER+, PR+, and HER2-) they benefit from

hormonal therapy and sometimes chemotherapy, Luminal B expressed genes (ER+, PR+, and HER2+) are less common and account for about 20 % of breast cancer. Luminal B carry a worse prognosis and has a higher recurrence rate compared with Luminal A, they benefit from chemotherapy and may also require hormonal or target therapy. The HER2+ subtype with (ER-, PR-, and HER2+) are likely to use both chemotherapy and target therapy in the patient's management plan. While Triple-negative/ basal subtype (ER -, PR-, and HER2-) are associated with the worse prognosis than hormone receptor-positive and they usually benefit from chemotherapy (58,198-200).

Once the diagnosis of breast cancer is finalized and the extent of disease and receptors status has been determined accurately, the treatment approach can be recommended. The exact treatment regimen will be determined by considering the clinical status of the patient, the age, related risk factors, and patient lifestyle. It is recommended that the patient be included in the discussion and be given an opportunity to assist in decision making, in the attempt to manage the disease. All breast cancer patients that are diagnosed with tumors positive for hormone receptors will receive endocrine therapy, while, triple-negative hormone receptor breast cancer patients are offered other chemotherapeutic modalities (58,198-200).

2.8.1 Early stage breast cancer

The early stage of breast cancer includes stage I, IIA, or a subset of stage IIB disease (T2N1) - for these cases, patients will undergo surgery of the primary tumor and lymph node biopsy/and or removal as a first treatment step. Moreover, both radiotherapy and chemotherapy may follow the surgical procedure based on tumor characteristics. However, patients with HER2-positive or triple-negative disease may be treated with neoadjuvant therapy first, followed by surgery for favorable results. The neoadjuvant therapy basically refers to providing treatment before the primary cancer surgery to shrink the tumor, whereas adjuvant therapy describes the administration of treatment after the primary surgical treatment to maximize the effectiveness of treatment (58).

2.8.2 Advanced breast cancer

This type of breast cancer includes locally advanced breast cancer and metastatic breast cancer types. They can be treated but are generally incurable, and treatment is provided to improve the patient's quality of life. Patients with advanced disease have a high risk of local recurrence and develop further metastatic lesions. Consequently, management must include systemic and loco-regional therapy (58).

2.9 Breast cancer and pregnancy

Although they are uncommon, they are the most common cancer in both pregnant and postpartum women, and they account for 2% of all breast cancer cases. Breast cancer cells have not been reported to transfer from the mother to the fetus, nor has termination of pregnancy been shown to have any effect on breast cancer outcome (201).

The diagnosis of breast cancer in pregnant females is by core biopsy, while ultrasound, x-rays with abdominal shielding, and non-contrast MRI are only used to determine the extent of disease when they are essential (202,203). Furthermore, bone scans (required in diagnosis in advanced stages of breast cancer) can only be performed during the postpartum period. The hormone receptors status is usually negative in pregnant women diagnosed with breast cancer, and the overall survival rates are generally worse than non-pregnant women in all stages. The treatment guidelines are as for non-pregnant women, however, both mother and fetus are taken into consideration when advising the management. In the first-trimester radical mastectomy with axillary staging is the treatment of choice, however, blue dye is contraindicated if SLNB is required. Technetium-99m is a safer option to detect involved lymph nodes. Adjuvant chemotherapy, when recommended, can be started in the second trimester, while radiation therapy is given only during the postpartum period. Trastuzumab (for HER2 positive breast tumors) and endocrine treatment are contraindicated during pregnancy due to the high risk of congenital deformities. After delivery, if the mother has been advised to receive chemotherapy, she should not breastfeed, and an alternative feeding method should be used (58).

2.10 Male breast cancer

Literature and research on screening methods, and trials for treatment options have largely focused on female breast cancer with less attention given to male breast cancer. This is understandable because of the low incidence of breast cancer in males. It is also more difficult to recruit enough participants for clinical trials because of the low incidence of this disease in men (3,4).

The overall incidence of breast cancer in males is less than 1% in the United States and Europe, while in Africa, a study done in Tanzania, reported male breast cancer incidence to be 6% of the total breast cancer population (204,205). A recent meta-analysis done in Sub-Saharan Africa found that the male to female ratio is higher in developing countries than developed countries. This would suggest that more research is required on male breast cancer, particularly in developing countries.

Men usually present complaining about a painless firm mass in the breast, and on clinical examination, a retracted nipple is commonly found by the physician. Around 40 % of males diagnosed with breast cancer already have an advanced stage where tumors have spread to axillary nodes. The late presentation is explained by the unawareness of men in developing breast cancer and thinking the disease is restricted to women. However, in comparison with the age of females developing the disease, men usually develop breast cancer about ten years older than women do (206,207).

As in female breast cancer, a tissue biopsy is advised with a mammogram of the breasts and ultrasound for the axilla to confirm the final diagnosis. Almost all invasive breast tumors affecting men are invasive ductal carcinoma and they account for more than 90 % of all breast cancer (206).

The primary genetic mutations in males diagnosed with breast cancer is associated with BRCA 2 and rarely BRCA 1 when compared with females carrying the mutated gene (208).

In males. alcoholic consumption, radiation exposure, and increase weight are common risk factors in developing breast cancer similar to females. Also, drugs or diseases that stimulate excessive estrogen levels such as hepatic dysfunction, thyroid diseases, orchitis, testicular injury, and inherited Klinefelter syndrome can all increase the risk of developing breast cancer in men (209).

Males diagnosed with breast cancer are treated similarly to postmenopausal females with breast cancer, depending on the tumor size, the number of lymph nodes involved, and hormonal receptor status. Modified radical mastectomy with axillary lymph node removal or lymph node biopsy is the type of surgical treatment performed for males. Furthermore, males diagnosed with breast cancer negative for hormonal receptors will benefit more from chemotherapy after removal of the primary tumor of the breast, while males diagnosed with hormone receptor positive breast cancer usually are given either Tamoxifen or undergo orchidectomy. Tamoxifen is the ideal hormonal therapy given to males (rather than aromatase inhibitors), due to the increased risk of developing breast cancer associated with aromatase inhibitors. Males usually have a poor outcome and a low survival rate compared to females diagnosed with the same stage of breast cancer (210-214)

2.11 Prevention and conclusions

The incidence of breast cancer is expected to grow and addressing the source of cancer is one of the primary tasks of public health to reduce incidence and mortality rates. Generally, there are three strategies to reduce the incidence and mortality associated with breast cancer (215).

At the moment there is no known way to prevent breast cancer, however, preventing known related risk factors, early detection of the disease and proper treatment are the only available management against breast cancer. The primary prevention strategy requires lifestyle modification which involves the direct avoidance or reduction in exposure to known carcinogenic factors. This can be achieved by maintaining moderate alcoholic intake, maintaining a healthy body weight, and performing regular physical activity,

these factors are associated with reducing breast cancer risk (6,138). However, although the literature has many studies showings the association between specific risk factors and the risk of developing breast cancer these studies are not considered conclusive enough to emphatically identify critical factors which cause breast cancer. Much more work is required in this area so that we can impact on the incidence of breast cancer like was done for lung cancer and smoking. Females at an increased risk because of the presence of an inherited mutated BRCA gene for instance could take medication like tamoxifen or perform surgical removal of breasts to reduce their risk.

Secondary prevention strategies help to reduce the mortality of breast cancer through screening modalities to detect early lesions before symptoms and signs appear. However, regular effective screening is a reality only in economically strong countries and are nearly completely absent in poor countries such as most of Africa. Therefore, disagreement about the age of commencement and the frequency of mammography screening led to the diversity of screening approaches in middle and low-income countries, because of the lack of resources (216).

The tertiary prevention strategy is in the form of cancer management plans such as cancer therapy and palliative care to improve the quality of life and survivorship; however, in low resource settings, availability may be limited or incomplete increasing both morbidity and mortality (61,217).

In conclusion, it would appear that based on the available information, the early detection and treatment of breast cancer is still is the best approach to reduce the mortality associated with this disease. Preventing breast cancer still requires extensive research to reduce the global breast cancer burden.

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CHAPTER THREE

THE PREVALENCE OF BREAST CANCER IN AFRICA:

A SYSTEMATIC REVIEW STUDY PROTOCOL

3.1 Background

The number of diagnosed females with breast cancer has grown over recent decades due to widespread screening and advances in clinical procedures in the methods of diagnosis (1) (2) (3) (4) (5). There are around 2.1 million women globally (2018), and it is estimated that it will reach up to 3.2 million new cases by the year 2050 (6) (7) (8). Across the world, the highest incidence rate of breast cancer is among developed countries. However, mortality rates of breast cancer have dropped in comparison with less developed countries (6), (9) (10) (11) (12). This decrease in mortality rates of breast cancer in developed countries is due to early diagnoses and proper management of patient, which prolongate the survival rates, 90% of females with breast cancer survive for more than five years after treatment in the United States and Canada, while in the Gambia, only 12% do survive (13) (14).

The African continent has the second largest number of people in the world, and it is expected to grow up to 4.1 billion by the year 2100. This fast growth in population and rising of life expectancy in Africa, lead to increased incidence of diseases. Among these diseases, breast cancer incidence in females has increased in most of the African countries. The latest data in 2012 has reported there where about 133,900 women newly diagnosed with breast cancer within 26 countries in Africa (15) (16). Females of white ethnicity living in South Africa have the highest incidence of breast cancer, probably due to adaptation of western lifestyle, increase in smoking and increase the use of hormonal birth control for family planning (9) (17) (18). Also, some studies have included male breast cancer in Africa, and they have reported that male-to-female ratio of breast cancer in the African countries is slightly higher than reported from western parts of the world (19).

Difficulties that are increasing cancer burden in Africa, cancer registry and high-quality data only covers 1% of the African population residing in Africa, and most of the available data are based on hospital records, missing patients that are unable to reach medical advice (20, 21) (22) (23). Therefore, the actual figures of breast cancer incidence, prevalence, and mortality rates cannot be measured accurately, leading

to unsuccessful management plans. Another problem facing the health officials is late detection of cancer, patients in most of the African countries first seek traditional herbal medication or consider cancer a destiny due to their firm religious belief (24) (25) (26) (27) (28). As a result, women will only seek medical advice from western medical services at a very late stage. By this stage, cancer may have already metastasized to the lymph nodes and then spread to the other parts of the body, severely limiting the treatment options available to patients at this stage (23) (29) (30) (31) (32). Also, war and political changes have caused instability in many parts of Africa, which has affected the health sector and prevented its progress. We are performing this systematic review to determine the prevalence of breast cancer in Africa and with the view that it will assist health professionals and policymakers in programming priorities for early detection, treatment and provide evidence for research in attempting to decrease the breast cancer burden in Africa.

Why is it important to do this review?

This systematic review will provide epidemiological data that can be used to guide health practitioners and educators for further studies needed in the field of breast cancer.

3.2 Objective

To conduct a systematic review of studies assessing the prevalence of breast cancer on the African continent.

3.3 Review question

What is the prevalence of breast cancer on the African continent?

3.4 Selection studies

3.4.1 Inclusion criteria

1. Studies describing the prevalence of breast cancer among male or female's participant, residing in Africa and diagnosed with breast cancer by histopathology reports.

2. We will include observational, population-based studies, trails, and cross-sectional studies of breast cancer.

3.4.2 Exclusion criteria

1. Studies with benign breast disease.
2. Studies which are not including African countries.
3. Studies which are including African population living other than African countries.
4. Studies that do not include histopathology diagnosis of breast cancer.
5. Narrative reviews, opinion pieces, and letters.
6. Studies based on hospital records without population screening.

3.5 Outcomes

Our outcome of interest includes the following

3.5.1 Primary outcomes

- Prevalence of breast cancer in both sexes
- Prevalence of breast cancer in females.

3.5.2 Secondary outcomes

- Prevalence of breast cancer by regions
- Prevalence of breast cancer in different settings.
- Study designs used in detecting breast cancer prevalence.

- Prevalence of breast cancer by different methods of diagnosis.

3.6 Search strategy for identification of relevant studies

Both published articles and unpublished papers will be considered with no time and language restrictions. The studies to be included will be selected using predefined search terms adapted for the database that will be used. Diagnosis of breast cancer will be based on histopathology reports. The search will be performed to all articles published in English or other languages related to the country original language.

Bibliographic databases

A. An expert librarian will help in the research strategy by checking the design that has been placed to ensure that there will be no missing articles or papers relevant to the title. We will start by checking the keywords that are used in the title and possibility of other synonymies.
B. An exhaustive search strategy with relevant subheadings will be used to identify all studies on the prevalence of breast cancer in Africa, in various databases like PUBMED/ MEDLINE, Cochrane database, EBSCO host (CINHAL/African Wide information), Web of Science, African index medics, Lilacs, and Scopus. Besides, we will conduct a manual search through the internet in google scholar, ProQuest and search World CAT for thesis, dissertation and conferences proceedings for any missing literature that was not published. The search terms will include both sexes male and females, prevalence and epidemiology, and we will specify the search to humans with the exception of children. The African search will include all countries of the African continent separately, and a further search by truncated names, e.g. (North Africa, Sub-Saharan region). We will consider the political name changes that occurred to countries over time, e.g. (Jamahiriya to Libya) and also the names of countries in different languages according to the country original language. We will search for studies from the references of articles that have been filtered for inclusion in the various database.
C. A clear, detailed search strategy is explained in appendix 1.

3.7 Selecting studies for inclusion

Two review authors will screen the titles and/or abstract of the studies that have been extracted using the search strategy independently. During the screening, the studies will be marked as either included, excluded, or pending. In the studies that are marked pending, a discussion will be undertaken to agree either include or exclude studies with a detailed explanation of reasons. For the studies that meet the inclusion criteria, a full text of these studies will be reviewed, and their details completed onto a data extraction form that will be designed by our team. The two reviewers should agree to the final number of studies. The search steps will be documented on PRISMA flow chart. (Figure 1)

3.8 Quality appraisal of included studies

The guidelines for evaluating prevalence studies by Hoy et al., modified by Werfalli and colleagues (33), will be used to measure the quality of studies through an external and internal validity as shown in (Table 1). The quantitative scoring system to the Risk of Bias criteria allocates four points of external validity and six points of internal validity. The scoring system tool categories high-risk studies as those with an overall score of 0-5 points, moderate risk as 6-8 and low risk >8 points. Two review authors will independently assess the risk of bias for each included study. In case of any disagreement, a third reviewer author will be consulted to resolve the disagreement.

3.9 Data extraction and management

Two review authors will independently extract data from the studies that are selected according to the criteria of inclusion and complete them in a data extraction form which is designed by the study team members. The data extraction form will first be piloted independently by two study team members using the same studies to assess comprehension. In case of discrepancies with data extraction, a third study team member will be consulted, and the difference resolved by consensus. The data extraction form is shown in (Table 2).

3.10 Data synthesis including assessment of heterogeneity

Data shall be presented in text, tables and figures documenting the numerators and denominators of breast cancer to be used for calculating prevalence. Data from outcomes of two or more similar studies will be pooled for analysis using a random-effects model where significant clinical and methodological heterogeneity exists between studies. Pooled statistics for breast cancer prevalence will be expressed as prevalence ratios with 95% confidence intervals (CI). Where a meta-analysis cannot be carried out due to significant heterogeneity, results will be presented in a narrative form.

Data will be pooled to assess heterogeneity, assessed firstly by visually inspecting the forest plots. Secondly, the Chi-squared test for homogeneity with a significance level set at 10% will be used. Finally, the I2 statistic will be used to quantify any statistically significant heterogeneity between study results and rated as 'low 'for ≤ 49% and 'moderate 'for 50-74% and 'high 'for ≥ 75% (34).

Efforts will be made to retrieve missing data by contacting the corresponding authors for the included studies. Where this is not possible, values will be imputed for primary outcomes in order to enable an intention-to-treat analysis. The other outcomes will be analyzed with only available data.

Subgroup analysis will be carried out based on the study design, study setting and demographic characteristics of participants including race, sex, the region of study, the facility available and the year of diagnoses if possible. Sensitivity analysis will be carried out where imputations were done for the primary outcomes and also to determine if the study designs, study period or publication type have an impact on the results of the meta-analysis.

3.11 Assessment of reporting biases

Asymmetry funnel plot will be constructed to assess the risk of publication bias per type of intervention if each intervention type included in the meta-analysis has over ten studies of varying sizes. Then it will be examined for asymmetry visually and statistically using the Egger test and Harbord test (35).

3.12 Reporting of this review

According to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement (36), the systematic review will be reported. A reporting guideline for systematic reviews of healthcare intervention and will include a PRISMA checklist.

3.13 Ethics and Dissemination

This systematic review will endeavour to fill in the gap of information on the prevalence of breast cancer on the African Continent. The study will provide prolegomena of evidence to future researches and will be disseminated by peer-review publication and conference presentations. Ethics approval is not required for this systematic review, patient's data will not be used, nor there will be any intervention with patients.

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Contributors

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None declared.

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Appendix 1: A descriptive detail of the search strategy.

MeSH in PUBMED/MEDLINE

Name used	Distributive electronic search terms.
Participants	"female" [MeSH] OR "Female" [All field] OR "Male" [MeSH] OR "Male" [All field] OR"Not Children"[MeSH] OR"[All field].
AND	
Breast cancer	"breast neoplasms"[MeSH Terms] OR "breast neoplasm" [All field] OR " human mammary carcinoma"[MeSH terms] OR"human mammary carcinoma"[All fields] OR "mammary neoplasms"[MeSH terms] OR "mammary neoplasms"[All fields] OR "ductal carcinoma"[MeSH] OR"ductal carcinoma"[All fields] OR "lobular carcinoma"[MeSH Terms] OR "lobular carcinoma"[All fields] OR "Infiltrating ductal carcinoma" [MeSH terms] OR"infiltrating ductal carcinoma"[All fields]
AND	
Prevalence	"epidemiology" [subheading] OR" epidemiology" [All fields] OR "prevalence" [MeSH] OR "prevalence" [All fields]
AND	
Africa	"lower income"[MeSH terms] OR"lower income"[All fields] OR "middle income"[MeSH terms] OR"middle income[All fields] OR "Africa"[Mesh terms] OR"Africa"[Al fields] OR "Nigeria"[tw]OR"Ethiopia"[tw]OR"Egypt"[tw]OR"Democratic Republic of Congo"[tw]OR"South Africa"[tw]OR"Kenya"[tw]OR"North Sudan"[tw]OR"South Sudan"[tw]OR"Algeria"[tw]OR"Uganda"[tw]OR"Morocco"[tw]OR"Mozambique"[tw]OR"Ghana"[tw]OR"Angola"[tw]OR"IvoryCoast"[tw]OR"Madagascar"[tw]OR"Cameron"[tw]OR"Niger"[tw]OR"BurkinaFaso"[tw]OR"Mali"[tw]OR"Malawi"[tw]OR"Zambia"[tw]OR"Senegal"[tw]OR"Chad"[tw]OR"Zimbabwe"[tw]OR"Rwanda"[tw]OR"Tunisia"[tw]OR"Somalia"[tw]OR"Guinea"[tw]OR"Benin"[tw]OR"Burundi"[tw]OR"Togo"[tw]OR"Eritrea"[tw]OR"Sierra Leone"[tw]OR"Libya"[tw]OR"Central African Republic"[tw]OR"Republic of Congo"[tw]OR"Liberia"[tw]OR"Mauritania"[tw]OR"Namibia"[tw]OR"Botswana"[tw]OR"Gambia"[tw]OR"Equatorial Guinea"tw]OR"Lesotho"[tw]OR"Gabon"[tw]OR"Guinea-Bissau"[tw]OR"Mauritius"[tw]OR"Swaziland"[tw]OR"Djibouti"[tw]OR"Reunion"[tw]OR"Comoros"[tw]OR"Cape Verde"[tw]OR"WesternSahara"[tw]OR"Mayotte"[tw]OR"Sao Tome and Principe"[tw] OR"Seychelles"[tw] OR"Saint Helena AscenSion and Tristan da Cunha"[tw]OR"North Africa"[tw] OR"Sub Saharan Africa"[tw] OR"East Africa"[tw] OR"West Africa"[tw]

- **Scopus/Africa and CINHAL/Web of science/Lilacs**

(Breast Neoplasms) OR (male breast neoplasms) OR (breast malignancy) OR (breast tumour) OR (breast tumour) OR (human mammary carcinoma) OR (mammary neoplasms) OR (breast carcinoma) OR (lobular carcinoma) OR (infiltrating ductal carcinoma) OR (ductal carcinoma)

AND

prevalence OR epidemiology

AND

Africa OR African OR (west Africa) OR (east Africa) OR (east Africa) OR (Sub Saharan Africa) OR (North Africa) OR (African Arab) OR Algeria OR Angola OR Benin OR Botswana OR (Burkina Faso) OR Burundi OR Cameroon OR (Canary Islands) OR (Cape Verde) OR (Central African Republic) OR Chad OR Comoros OR Congo OR Democratic Republic of Congo OR Djibouti OR Egypt OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR (Ivory Coast) OR (Cote d'Ivoire) OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR (Sao Tome) OR Senegal OR Seychelles OR (Sierra Leone) OR Somalia OR (St Helena) OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR (Western Sahara) OR Zaire OR Zambia OR Zimbabwe.

- **Manuel search for articles, conferences, Books and thesis by World CAT and ProQuest thesis and dissertations.**

- **Google Scholar search.**

Appendix 2: Table 1

External validity

1. Was the study's target population a close representation of the national population in relation to relevant variables? (1 point)
2. Was the sampling frame a true or close representation of the target population? (1 point)
3. Was some form of random selection used to select the sample, OR was a census undertaken? (1 point)

4. Was the likelihood of nonresponse bias minimal? (1 point)

Total points (4 points)

Internal validity

1. Were data collected directly from the subjects (as opposed to a proxy)? (1 point)
2. Was an acceptable case definition used in the study? (1 point)
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability? (1 point)
4. Was the same mode of data collection used for all subjects? (1 point)
5. Was the length of the shortest prevalence period for the parameter of interest appropriate? (1 point)

6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? (1 point)

Total points (6 points)

Appendix 3 Table 2: Systematic review data extraction form

A. Source:

Reviewer title	Prevalence of breast cancer in the African continent.
Study ID	Muna Abulkasim
Name of person extracting data	
Initial of person extracting data	
Date of filling the form	——/——/20——
Title of article	
Reference citation	
Published	Yes, No Name of Journal:
Study author contact details	
Publication type	Full-text Abstract Book Conference Thesis Others:
Country of origin	
Language of study	Eng Fre Ger Arabic Africans Other Translation: Yes No
Year of publication	——/——/——
Reference of potentially eligible studies from the reference list	
Funding	Yes No Source:
Notes	

B.Study eligibility:

Study design	Cross-section Population-based registry Others
Study period	
Data source	Hospital: 1ry 2ry 3ry Private Survey Others
Population study	Total Specific group Others
Setting	rural urban not mentioned
Prevalence	Yes No Unclear
Study	Included Excluded Pending
Excluded reason	
Pending	
Notes	

Hoy guide Q	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Points/										

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

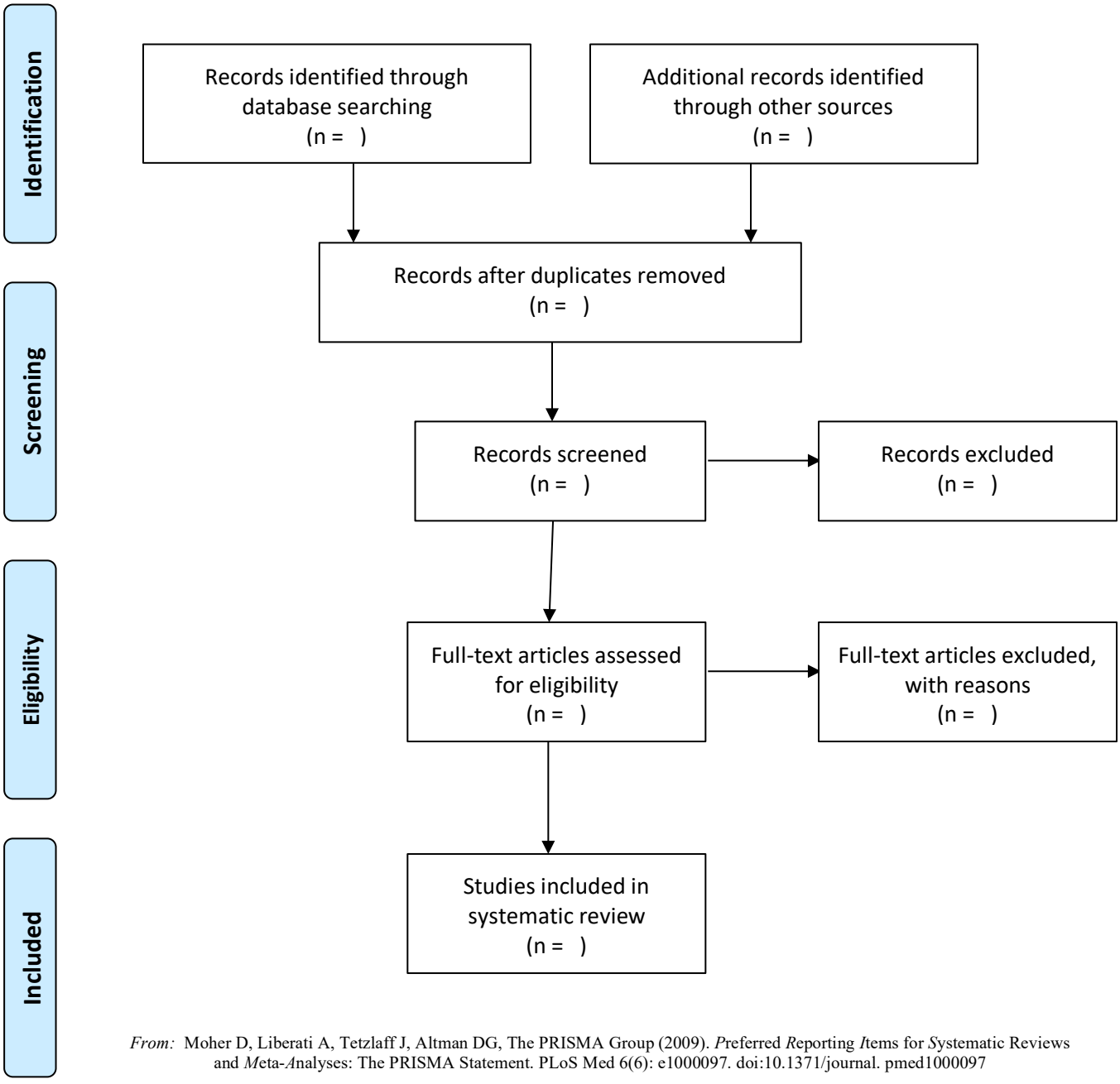
C. Study characteristic:

Type of screening	BSE CE U/S Mammo Histopathology Other
The common type of breast cancer	
The common site of breast cancer	
Age group	M / Mean F /Mean Both /Mean
Stage of disease	Early Late Unclear I II III IV
ER / PR / HER 2	Luminal: A B TN/B-L N-L Her2-enriched
Genetic studies available	Yes No Not mentioned
Treatment	Surgical Chemotherapy Radiotherapy Hormonal
Follow up	Yes No Not mentioned
5-year survival	Yes No Not mentioned
Gender	M / Denominator F / Denominator Both / Denominator
Ethnicity	
Education of patient	non 1ry 2ry 3ry Other

D. Results:

Measure of the prevalence	Crude measure Adjust measure
If adjusted what factors were adjusted for in this study (list):	
Reported measure of the prevalence:	
Author was contacted	Yes No
Author reply	Yes No
Comments	

Appendix 4 PRISMA 2009 Flow Diagram (Figure 1)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal. pmed1000097

CHAPTER FOUR

THE PREVALENCE OF BREAST CANCER IN AFRICA:

A SYSTEMATIC REVIEW AND META-ANALYSIS

Abstract

Introduction

Breast cancer is well-known globally and remains one of the principal health concerns affecting women, and a rare malignancy in men. Although, there has been significant progress made in prevention strategies such as early detection and better treatment in most developed countries, incidence and mortality rates of breast cancer continued to rise. The rise is significant in Africa, a continent low in resources with a growing and ageing population exposed to risk factors leading to developing the disease. We have percolated this systematic review and meta-analysis as a reliable form of medical evidence to measure the prevalence of breast cancer in Africa.

Methods

We searched, using an African search filter with no time limits, electronic databases, grey literature and reference lists for eligible primary studies meeting pre-specified criteria. Two authors independently screened the search outputs, selected studies, and extracted data; resolving discrepancies by consensus and discussion. Using Stata software, we applied the random-effects meta-analysis model to aggregate prevalence estimates with 95% CI incorporating the Freeman-Tukey transformation to account for between-study variability.

Results

The overall prevalence rate of breast cancer in Africa was 0.30 [95% CI, 0.26 to 0.34] (22 studies, n=10,795). The prevalence rate of breast cancer for African females was 0.49 [95% CI, 0.38 to 0.62]. South African region had the highest breast cancer prevalence rate, 0.65 [95% CI, 0.24 to 1.26], while the lowest rates of breast cancer were from Central African regions. The use of mammography yielded higher rates of detection, (0.63 [95% CI, 0.46 to 0.82]), in comparison with clinical breast examination (0.31 [95% CI, 0.22 to 0.42]).

Conclusions

The clinical picture of breast cancer in Africa differs from Western countries due to the high proportion of patients developing the disease at a younger age and seeking management care at an advanced stage. Currently, there exists no specific breast cancer registry designed specifically for any African patients living in Africa and thus, prevalence studies of breast cancer from African countries are limited. The results emphasize the need for resources to further research the causes of breast cancer and affordable alternative methods for early diagnosis, especially given the low resource setting. The study contributes evidence to the current situation on breast cancer in Africa and stresses the need for health professionals and policymakers in programming to priorities early detection, treatment and ominous need for evidence to decrease the breast cancer burden in Africa.

Keywords: breast cancer, epidemiology, prevalence, female, male

4.1 Introduction

Mammary cancers are the most frequently detected malignancies in women and are considered one of the leading causes of death around the world (1) (2) (3). According to the global geographical distribution, breast cancer incidence is highest among Australia/New Zealand, Northern America, and North-Western regions of Europe (1, 3). This high incidence is reflected by the high prevalence of risk factors and genetic mutation in specific ethnic groups, regardless of the high incidence, the mortality rates from this disease have declined on account of advances in early detecting plans and availability of treatment option for controlling the cancer growth among these regions resulting in more women surviving with the disease (1) (4).

In Africa, women develop the disease at a younger age and present at a late stage in comparison with western countries (4) (5) (6) (7). Due to a lack of awareness, late-stage presentation, lack of early detection programs, limitation of standard pathological services and inaccessible treatment opportunities, mortality rates of breast cancer have increased (7) (8) (9) (10). Therefore, only a minority of women diagnosed with early breast cancer in most African countries. Since increasing and ageing of the population on the African continent, change of environment, adapting of new lifestyles, and exposure to cancer risk factors, more and more women will develop breast cancer, thus causing a rise in the cancer burden (11) (12) (13) (14) (15) (16) (17)(18).

The definition of prevalence rate is the total number of newly diagnosed people and people who are alive with the same disease at a specific time. Prevalence studies are useful in informing health care professionals of disease geographical distribution and in monitoring trends over time and provide information for further etiological studies and investigate the causes of disease.

4.2 Aim

We have percolated this systematic review as a reliable form of medical evidence to measure the prevalence of breast cancer in Africa, with the intention to document the status of the current situation. This study is aimed at assisting health professionals, government, and policymakers to

inform, plan the selected interventions and to deliver a better health care service for the general population of Africa.

4.3 Methods

This systematic review protocol has been published in the PROSPERO International Prospective Register of Systematic Review (http://www.crd.york.ac.uk/PROSPERO), with a registration number CRD42017080780 and was checked according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2015 Statement (19) (20) in (Appendix1). The full detail of the protocol is available in Chapter Three.

4.3.1 Criteria for included studies

Types of studies

Cross-sectional, observational, randomized control trails, and population-based studies were selected and included in this systematic review. Studies with no pathological evidence of diagnosis of breast cancer, studies based on only hospital or laboratory/Pathology records without population screening were excluded (studies with no denominator).

4.3.2 Types of Participants

Studies described the prevalence of breast cancer among male or female participants, residing in Africa and diagnosed with breast cancer by histopathology tests.

4.3.3 Types of outcomes

Primary outcomes:

- Prevalence of breast cancer in both sexes
- Prevalence of breast cancer in females.

Secondary outcomes:

- Prevalence of breast cancer by regions
- Prevalence of breast cancer in different settings.
- Study designs used in detecting breast cancer prevalence.
- Prevalence of breast cancer by different methods of diagnosis.

4.3.4 Search strategy for identification of relevant studies

A comprehensive search was conducted from both published and non-published studies, with no language restriction and time limitation by both authors [MA, LA]. An expert librarian helped with the research strategy. Subheadings were used to identify all studies on the prevalence of breast cancer in Africa of various databases like PUBMED/ MEDLINE, Cochrane database, EBSCO host (CINHAL/African Wide information), Web of Science, African index medics, Lilacs, and Scopus. Also, we conducted a manual search using google scholar, ProQuest, and search World CAT for theses, dissertations, and conference proceedings for any literature that was not published.
Search terms included both male or female, prevalence and epidemiology and had limited the search to humans, except for children. The African search included all countries on the African continent separately, and a further search performed by truncated names, e.g. (North Africa, Sub-Saharan

region). We considered the political name changes that occurred to countries over time, e.g. (Jamahiriya to Libya) and also the names of countries in different languages according to the country's original language. Finally, we searched studies from the references of articles that have filtered from the pooled studies in the various databases. A descriptive detailed search strategy is explained in Appendix 1 - chapter 3.

4.3.5 Data extraction and management

The two authors, MA, and LA independently extracted data from the studies selected according to the inclusion criteria onto a data extraction form designed by the study team members.

The data extraction form was first piloted independently by the team members MA and LA, together with author ME as the third author reviewing the data extraction form. The modified data extraction form is shown in Appendix 3 - chapter 3.

4.3.6 Selecting studies for inclusion

MA and LA screened the titles and abstracts of all the identified records from both the database searches, and the additional manual searches pooled into EndNote with automatic removal of duplicates. The screened studies were marked as either included, excluded, or pending by the two authors separately MA and LA. In the studies that are marked pending, a discussion undertook to agree either to include or exclude the studies with a detailed explanation of reasons. A third reviewer ME was consulted with the discussion and revision of the inclusion criteria until an agreement reached to the final number of studies. We used a flow diagram from PRISMA guidelines for this systematic review for all studies selected and summarized in Appendix 4 – chapter 3.

4.3.7 Quality appraisal of included studies

We evaluated quality assessment using the tool by Hoy et al. modified by Werfalli and colleagues (21). The scoring system categorises studies as high-risk (overall score of 0-5 points), moderate risk

(6-8 points), and low risk (>8 points). The Quality assessment criteria for prevalent studies with scoring (Red -high risk, Yellow -medium risk, and Green low risk can be found in appendix 5. Studies using randomized trial designs were assessed using the Cochrane tool for the risk of bias (appendix 6).

4.3.8 Data synthesis including assessment of heterogeneity

Data were analysed using Stata statistical software. Firstly, prevalence estimates were recalculated using the given numerator and denominator for each study (Table 5 explains all the collected information from each study in the result section). Then, the overall prevalence from the eligible studies of the systematic review was calculated including 95% confidence intervals (CI). Secondly, we estimated the prevalence for each subgroup and analysed regions within the African continent and settings. We also stratified the prevalence results according to the female gender, type of screening methods conducted in the selected studies outcomes, and study design.

In addition, heterogeneity between the studies were assessed by using the chi-square test and I^2 statistic; we regarded heterogeneity as substantial when I^2 was more than 50% (20).
Lastly, we assessed all the included studies by using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for the certainty of evidence. Findings of the assessment across studies using the GRADE are judged as having high, moderate, low or very low levels of certainty. Certainty lowers each time there is a serious concern with the risk of bias, inconsistency, indirectness, imprecision, and publication bias. High certainty evidence implies that further research is very unlikely to change our confidence in the estimate of effect. Moderate certainty of evidence means that further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. When the evidence is considered of low certainty if further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. While very low certainty if we have very little confidence in the effect estimate (22) (23) (24).

4.4 Results

4.4.1 Description of the studies

Our results following a comprehensive search strategy yielded 10,067 records that were pooled together into Endnote reference management software. A total of 1067 studies were identified as possibly meeting with our inclusion criteria, after screening titles and removal of duplicates electronically. Thirty-four studies we eventually determined needing review of full text, resulting in the removal of 12 articles; the excluded studies reasons shown in table 2. Thus, 22 studies are included in the quantitative systematic review and meta-analysis. Steps of the search results are documented in the flow diagram from the PRISMA chart (figure1).

Study description: Details of the included studies gathered measuring the prevalence of breast cancer are shown in Table 1. The main points include author and the year of publication, the study period, study design, the type of participant, the country of origin, type of setting, the method used in the diagnosis of prevalence for each study.

Language Restriction: Out of the twenty-two articles, 19 were in English leaving with three French studies requiring translation into English (25) (26) (27).

The English language studies are: (28) (29) (30) (31) (32) (33) (34) (35) (36) (37) (38) (39) (40) (41) (42) (43) (44) (45) (46)

Study design: Most of the studies included are screening in nature (cross-sectional studies) and retrospective. Only two studies provided prevalence report from trail studies (28) (29).

Participant characteristics: 19 studies have included only female participants in the screening and only 3 Studies of the total 22 combined both sexes in the detection of breast cancer.

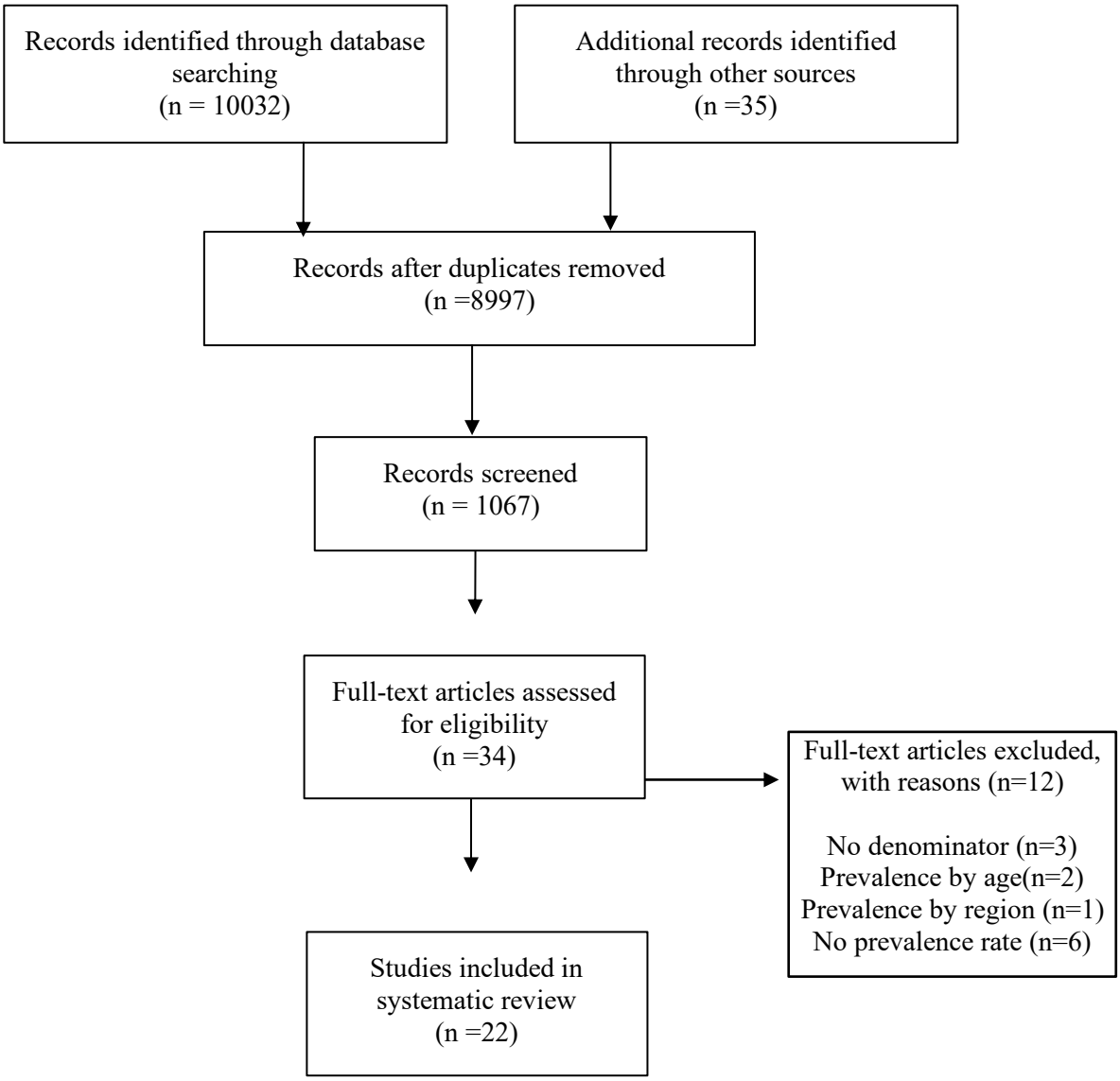


Figure 1 PRISMA 2009 Flow Diagram (search results).

Age characteristics: The youngest age screened for breast cancer started from 18 years, while the oldest age groups, including women of 90 years. A total of 9 studies have calculated the mean age of participants, and the rest gave the range of screening except for one study, which has not mentioned the age group (29).

Study origin: All the studies conducted in Africa met our inclusion criteria (Figure 2). The majority of the studies were from North Africa {Three studies from Morocco (30) (31) (32) Two studies from Sudan(33) (34), Three studies from Egypt (28) (35) (36) and Three studies from Tunisia (25) (26) (27) . West Africa represented by five studies {two from Nigeria (37) (38), one study from Cameroon (39) and two from Ghana (40) (41). A study each from Tanzania (29), Kenya (42) conducted from East Africa. Central Africa region had included only one study from DR Congo (43). The remaining three studies were from RSA (44) (45)and Zambia (46).

Only two studies have not mentioned their setting origin. Out of the 20 studies, there were seven performed in rural parts of the continent.

Study period: The earliest study was conducted in 1999 to calculate prevalence results (40) and our search ended by the end of the year 2018. The most prolonged study period calculated the prevalence for ten years (44). Both studies (28) (35) have not mentioned any information regarding the start and end of the study period.

Study samples: The most significant study sample covered three million of its population (30), while the smallest sample included 1094 recruited female (42).

Prevalence count: Result of the prevalence of breast cancer was available in most of the studies in our review, However, when the final figure was not available calculation was performed since both the nominator and denominator are present in all the included studies as shown in Table 1 below.

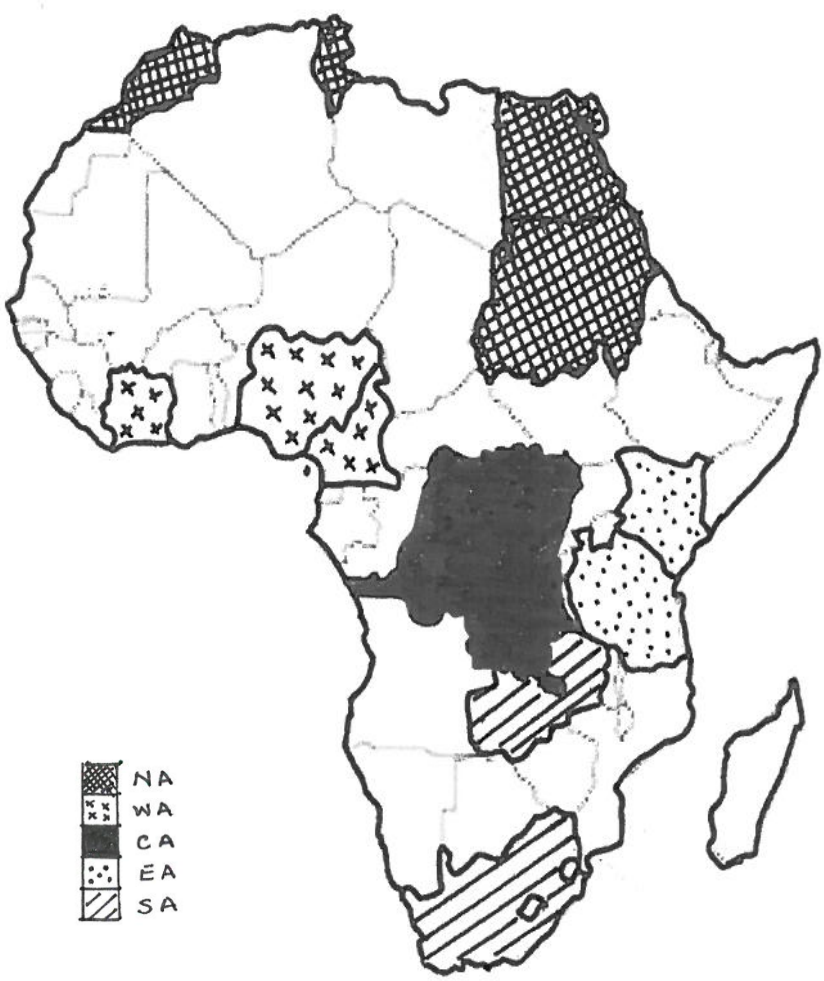


Figure 2: Distribution of Prevalence of breast cancer in the African countries.

Table 1: Summary of the Included studies

Author	country	Setting	study period	study design	gender	common type	age specific	Method used in diagnosis	n (m) n(f)	N
Abuidris,2013	Sudan	rural	2010-12	CS-pilot	F	-	>18	CBE, MMG, U/S	17	10 309
Agbo,2014	Nigeria	urban	2007-11	Retro	F	Invasive ductal3,4	48,2	-	288	2 781 416
Agyei-Frempong, 2008	Ghana	u/r	1999-2002	CS	F	-	47.77,	-	102	15 221
Apffelstaedt,2014	RSA	-	2011-12	CS/pilot	F	-	40-70	MMG	10	2 712
Apffelstaedt,2014	RSA	-	203-2012	CS	F	Invasive	>40	MMG	43	3 774
Basu, 2018	Morocco	u/r	2015-16	SC	F	-	40-60,49.5	CBE,	1,048/1,238	1,000,000/1,600,000
Boulos,2005	Egypt	urban	-	Trail	F	-	35-64	CBE, MMG, U/S	20	4 116
Chraka, 2018	Morocco	rural	2012-14	Retro	F	-	45-69	CBE,	224	184 951
Denewer,2010	Egypt	rural	2-year study	CS/pilot	F	G 2,3	46	CBE, MMG, U/S	18	5 900
El-Fakir, 2015	Morocco	urban	2009-11	Retro/SC	F	-	45-70	CBE, MMG, U/S	4	2 350
Frikha,2013	Tunis	urban	2004-10	CS/pilot	F	-	>45-86,51.5	MMG	56	10 000

Kribi,2003	Tunis	urban	1995-97		F	Invasive	40-70	MMG	10	2 200
Mvila,2014	Congo	urban	2010-12	CS	F	Invasive	>18	CBE, MMG, U/S	100	4 315
Naku,2016	Ghana	rural	2007-8	CS	F	Invasive ductal	25-54	CBE, MMG, U/S	24	3 000
Ngoma,2014	Tanzania	rural	2009-11	TRAIL	F/M	-	-	CBE, biopsy	42	10 979
Ozolio,2014	Nigeria	rural	2009-10	Pros/CS	F	-	>35,12-90	MMG	29	2 095
Pinder,2018	Zambia	rural	2008	CS	F	-	35,9	CBE, U/S	6	1 129
Saeed, 2016	Sudan	u/r	2009-13	CS/Pop	F/M	-	36-45	-	F=5,500/M=250	36 163 778
Sando,2018	Cameroon	u/r	2008-15	CS	F/M	DuctalG2,3	47,9	-	M=15/F=1470	22 179 707
Salm,2008	Egypt	urban	2007-2008	CS/pilot	F	Invasive ductal	>45	MMG	159	20 098
Sayed,2016	Kenya	u/r	2015	CS/pilot	F	Invasive	m=36.5	CBE, MMG, U/S	15	1 094
Zaanouni,2009	Tunis	urban	2004-06	CS/pilot	F	Invasive	40-69/m=48.9	MMG	27	5 325

CS=cross-sectional studies, MMG =mammograms, U/S = ultrasound test, u/r = both urban and rural, CBE = clinical breast examination, Pop =population-based screening.

Table 2 Excluded studies with reasons

Author	Reason of exclusion
Adetifa,2009	Prevalence by age
Amando,2015	No prevalence of breast cancer
Amir, 1994	No prevalence of breast cancer
Balekouzou,2016	No denominator
Bowa 2008	No information on prevalence
Enow,2012	Total cancer prevalence
Errahhali,2016	Prevalence of cancer by region in the country.
Mayi-Tsonga,2009	No denominator
Obossou 2017	No prevalence of breast cancer
Okoye, 2017	Prevalence by age only
Sando,2014	No prevalence rate
Woldu,2017	No denominator

Reasons for the excluded studies based on the title, these studies were not conducted in Africa or were not including African patients diagnosed with breast cancer. Studies that were excluded based on abstracts they were not including prevalence rate, or their study design did not match our included criteria. Finally, the main reason for excluding articles that were reviewed by full text with an explanation of the reason for exclusion shown in (Table 2).

4.4.2 Risk of bias assessment

4.4.2.1 Assessing risk of bias of studies

The risk of bias assessment was judged by using Hoy criteria modified by Werfalli and colleagues for each domain of the 20 included studies (25) (26) (27) (30) (31) (32) (33) (34) (35) (36) (37) (38) (39) (40) (41) (42) (43) (44) (45) (46).

The tool included ten items and rated: 0-5 high risk [Red], 6-8 moderate risk [Yellow] and more than 8 a low-risk study [Green]. The result of the risk of bias assessment for the included studies shown in (Table 3).

No studies from our included articles were at high risk. Three studies were of low risk (27) (34) (36), and the rest of moderate risk bias (Table 3). Studies(30) (36) (37) (41) represented a close sample to the target population. All the included studies have been using random selection in their sample or census was undertaken. Of the 20 articles, only 7 had a minimal of non-response bias. All studies data that are included are collected directly from subjects. According to the study instrument that measured the parameters (30) (34) (40) were not mentioned, while studies (31) (32) (35) (36) (42) (43) (46) are not valid and reliable. All the included studies nominators and denominators were available to calculate the prevalence of breast cancer.

4.4.2.2 Assessing risk of bias using Cochrane tools

We extracted prevalence data from two experimental studies assessing interventions of screening (28) (29) of breast cancer from trials conducted in Africa. These were appraised separately using the Cochrane assessment tool for the risk of bias (20). (Figure 3, Table 4)

Generation of allocation sequence and Allocation concealment for both studies were deemed to be of low risk. Risk of selective reporting was low (28) and unclear (29) in the respective studies. Blinding: was not described in sufficient detail and was marked unclear. Incomplete outcome: both studies were low risk of bias.

Table 3: The risk of bias assessment table for observational studies

Country	*Author/Year*	*Risk of bias 1*	*Risk of bias 2*	*Risk of bias 3*	*Risk of bias 4*	*Risk of bias 5*	*Risk of bias 6*	*Risk of bias 7*	*Risk of bias 8*	*Risk of bias 9*	*Risk of bias 10*	*Overall risk of bias*	*Rating score*
Cameroon	Sando	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	9
DRC	Mvila	NCS	NCS	Low	High	Low	Low	NCS	Low	Low	Low	Moderate	6
Egypt	Salem	NCS	Low	Low	NCS	Low	Low	Low	Low	Low	Low	Moderate	8
Egypt	Denwar	NCS	High	Low	NCS	Low	Low	High	Low	Low	Low	Moderate	6
Ghana	Agyei-F	NCS	NCS	Low	NCS	Low	Low	NCS	Low	Low	Low	Moderate	6
Ghana	Naku	Low	Low	Low	NCS	Low	Low	Low	Low	Low	Low	Moderate	8
Kenya	Sayed	NCS	NCS	Low	Low	Low	Low	High	Low	NCS	Low	Moderate	6
Morocco	El Fakir	High	High	Low	High	Low	Low	High	Low	Low	Low	Moderate	6
Morocco	Charaka	NCS	Low	Low	High	Low	Low	High	Low	Low	Low	Moderate	7
Morocco	Basu	Low	Low	Low	NCS	Low	Low	NCS	NCS	Low	Low	Moderate	7
Nigeria	Agbo	Low	High	Low	High	Low	Low	Low	Low	Low	Low	Moderate	8
Nigeria	Ozolio	NCS	High	Low	NCS	Low	Low	Low	Low	Low	Low	Moderate	7
RSA	Apffel (i)	NCS	NCS	Low	Low	Low	Low	Low	Low	Low	Low	Moderate	8
RSA	Apffel (ii)	NCS	NCS	Low	Low	Low	Low	Low	Low	Low	Low	Moderate	8
Sudan	Abudris	NCS	Low	Low	Low	Low	Low	Low	Low	Low	Low	Moderate	8
Sudan	Saeed	Low	Low	High	Low	NCS	Low	Low	Low	Low	Low	Low	9
Tunisia	Kiribi	NCS	NCS	Low	NCS	Low	Low	Low	Low	Low	Low	Moderate	7
Tunisia	Zaanoni	NCS	Low	Low	Low	Low	NCS	NCS	Low	Low	Low	Low	9
Tunisia	Farika	NCS	Low	Low	High	Low	Low	Low	Low	Low	Low	Moderate	8
Zambia	Pinder	NCS	NCS	Low	High	Low	Low	NCS	Low	Low	Low	Moderate	6

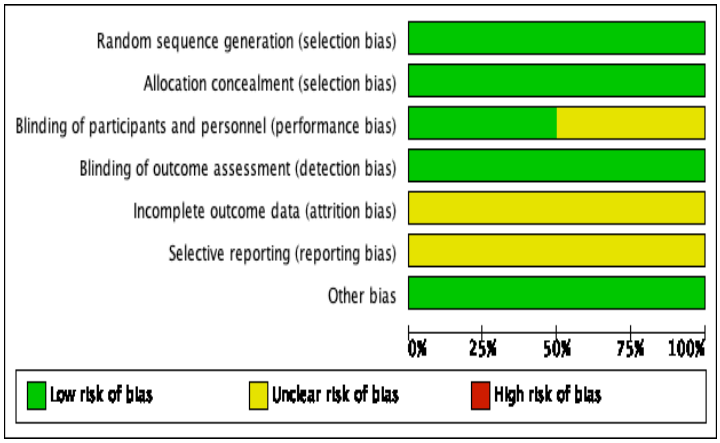


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Table 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Author	A	B	C	D	E	F	G
7.Boulos,2005	Low	Low	Low	Low	Un	Un	Low
15.Ngoma, 2014	Low	Low	Un	Low	Un	Un	Low

Un = unclear A= Random sequence generation, B=Allocation concealment, C=Blinding participant, D=Blinding of outcome assessment, E=Incomplete outcome, F=Selective reporting, G=Other bias

4.4.3 Missing Data

In this systematic review, none of the authors needed to be contacted since we did not find any missing data.

The judgment of the certainty of evidence by using the GRADE approach of included studies. Among the intervention studies, we judged the certainty of the evidence as moderate for detecting the prevalence of breast cancer. We assessed the certainty of evidence as moderate for the observational studies and the combination of total included studies; we assessed the certainty of evidence as moderate — our main concerns with the evidence related to study limitations.

4.4.4. Data synthesis

4.4.4.1 Overall synthesis

The overall finding in this systematic review of the prevalence of Breast Cancer in Africa is 0.30 per cent, 95% Confidence Interval (CI) (0.26-0.34) test for heterogeneity, $I^2 = 99.70\%$; 22 studies, N= $6x10^7$ participants (Figure 4).

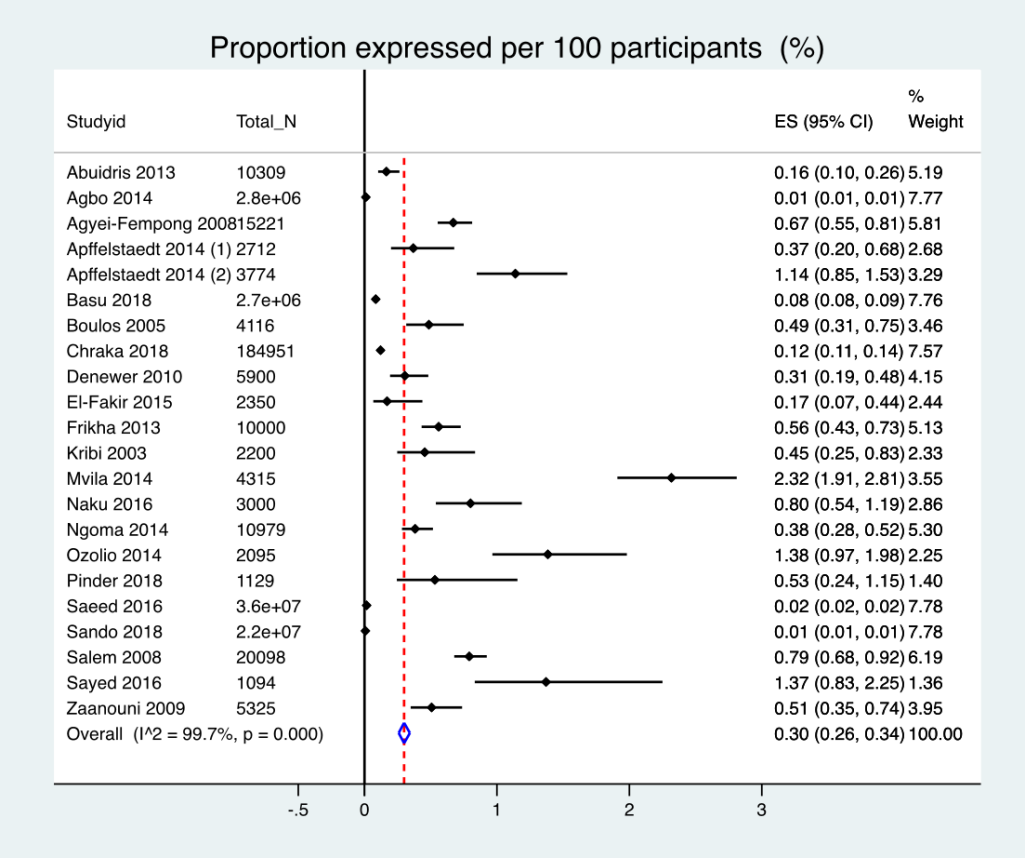
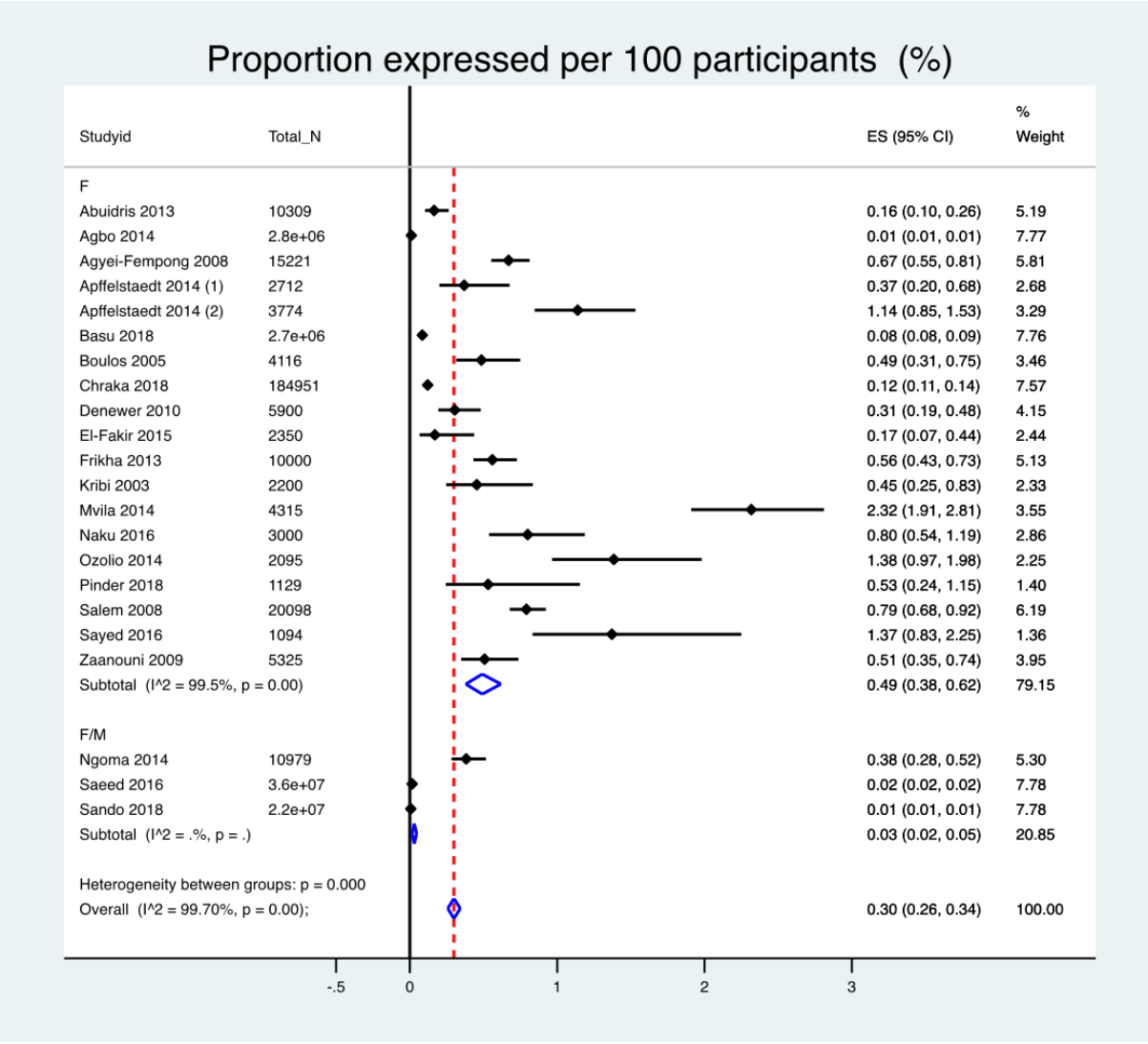


Figure 4. The overall prevalence of breast cancer in Africa.

4.4.4.2 Gender analysis

Pooled prevalence estimates by gender revealed 0.49% (95% CI, 0.38 to 0.62) in females versus 0.03% (95% CI, 0.02 to 0.05) in studies reporting males and females as a single entity. (figure 5).



NB: F= female gender, M=male gender. F/M= both sexes included in the studies.

Figure 5. The prevalence rate of breast cancer in African females.

4.4.4.3. Regional analysis

When considering the studies on a regional basis, rates for breast cancer were highest in the south (0.65%, 95% CI (0.24 to 1.26) and western (0.55 (95% CI (0.03 to1.65) regions of Africa (Figure 6). While the overall prevalence in central Africa was practically zero, one of the two studies comprising the meta-analysis had a high prevalence, probably due to sample size being small in comparison to the other. (Test for heterogeneity, $I^2 = 99.70\%$)

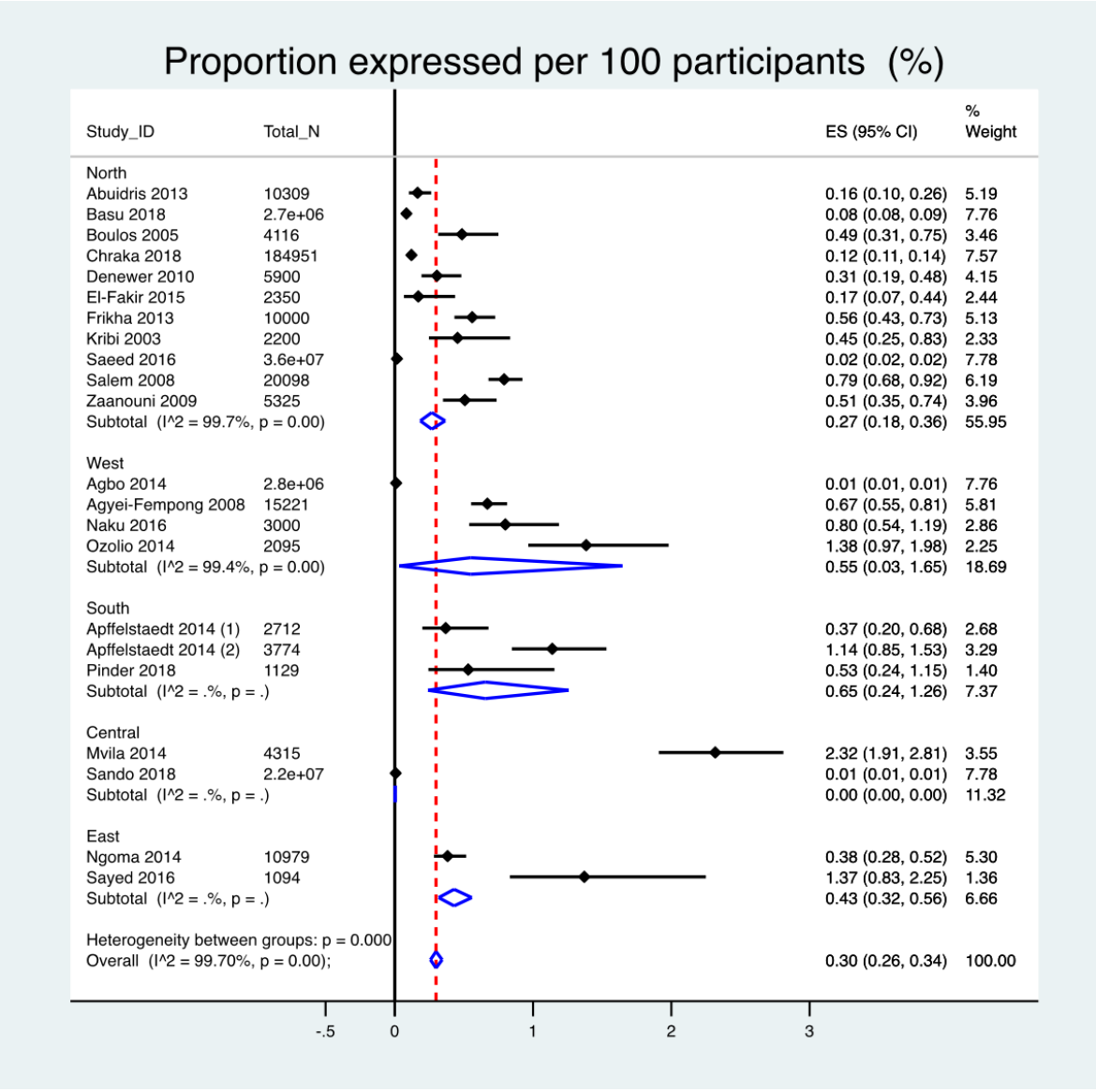
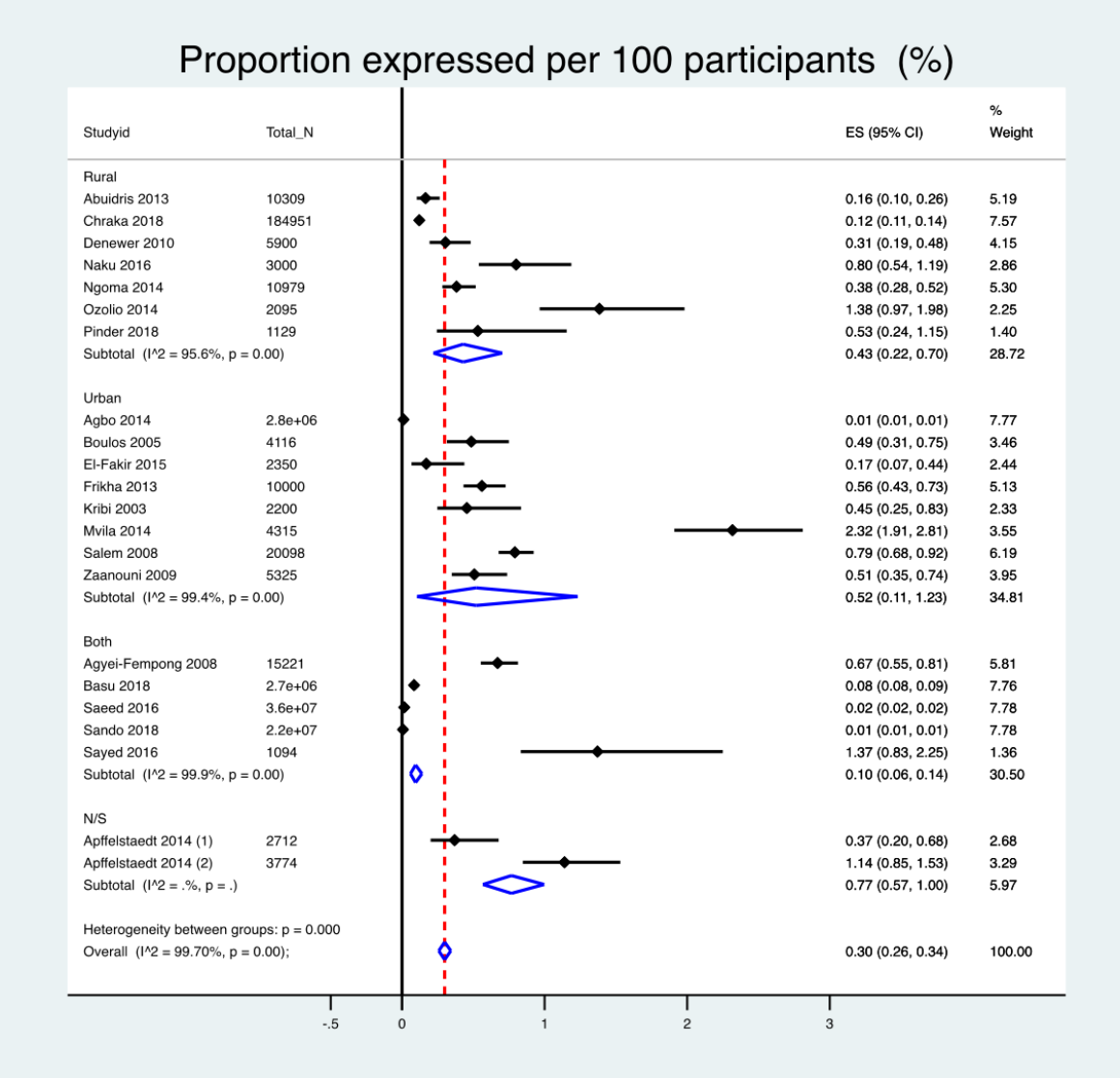


Figure 6. The prevalence rate of breast cancer in the five African regions.

4.4.4.4 Urban vs Rural

The pooled prevalence estimates by authors' descriptions of geographical settings as being rural and urban were 0.43% (95% CI, 0.22 to 0.70) and 0.52% (95% CI, 0.11 to 1.23) respectively (figure 7). While studies that reported prevalence estimate in both urban and rural geographical regions showed a pooled prevalence of estimate of 0.10 (95% CI, 0.06 to 0.14).

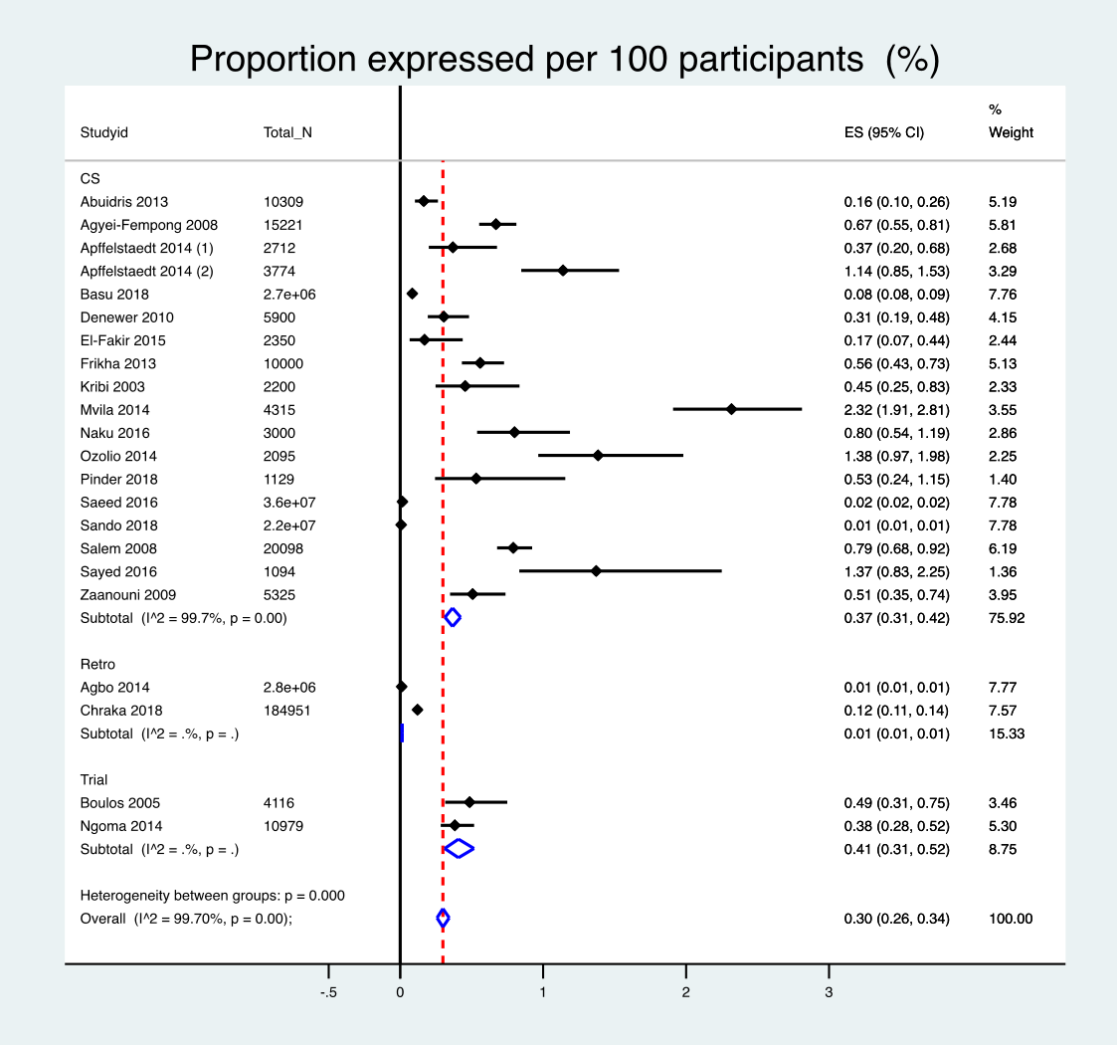


NB: N/S= not specific, not mentioned.

Figure 7: The prevalence of breast cancer by urban vs rural settings

4.4.4.5. Study design

The prevalence estimate for breast cancer in this review was provided by cross-sectional, retrospective and trial studies. There was a difference between the pooled prevalence estimates for the different study types ranging from 0.01 (95% CI, 0.01to 0.01) for retrospective study designs, 0.37 (95% CI, 0.30 to 0.42) for cross-sectional, and 0.41 (95% CI, 0.31 to 0.52) for trials (figure8).

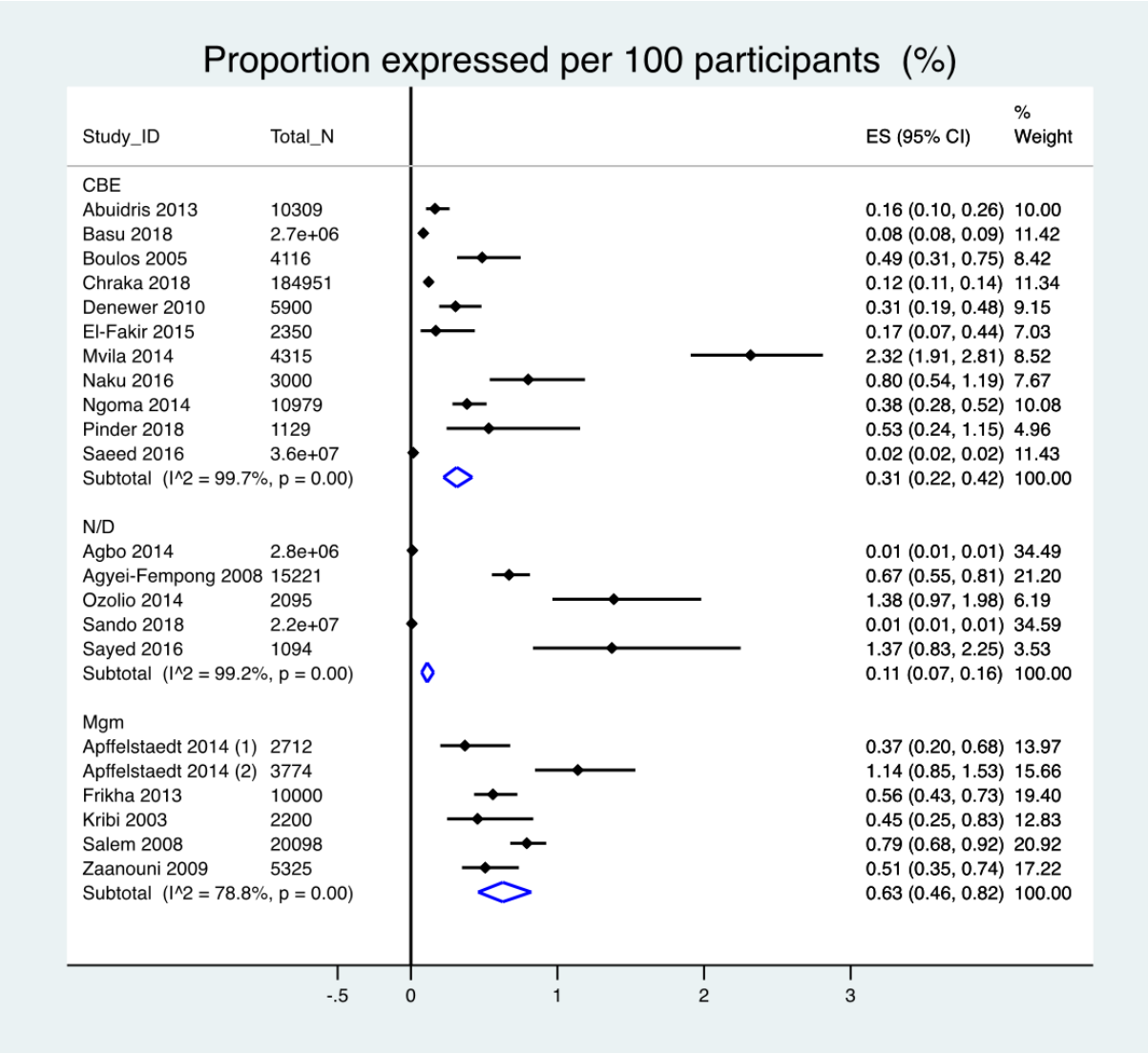


CS= cross-sectional studies, Retro=retrospective studies

Figure 8. The prevalence rate of breast cancer in different study designs.

4.4.4.6. Methods used in diagnosis

When considering the method of breast cancer diagnosis, the pooled prevalence estimates for studies using mammography was higher than for clinical breast examination, 0.63 (95% CI, 0.46 to 0.82) and 0.31 (95% CI, 0.22 to 0.42) respectively. (Figure 9).



CBE=Clinical breast examination, N/D=Not detected, MMG=Examination by mammograms

Figure 9. The prevalence rate of breast cancer using different screening methods.

4.4.5 Investigating Heterogeneity

There was notably large heterogeneity across the studies comprising our meta-analysis. Subgroup analysis did not significantly change the heterogeneity estimate.

4.5 Discussion

Summary of main results

This systematic review of African studies, using a comprehensive search strategy across a number of databases and grey literature, without language or specific date restrictions, found the prevalence of breast cancer in Africa to be 0.3%. Our primary aim in this systematic review was to determine the prevalence of breast cancer on the African continent in both sexes and for female patients precisely. We also sought to report (1) regional differences, if any, (2) which of the African countries provided reliable data, (3) differences in prevalence rates in urban and rural settings and finally, (4) the prevalence rate of breast cancer according to study design and method used in detecting breast cancer from the selected articles.

Overall completeness and applicability of evidence

Our pooled results calculation of the prevalence rate of breast cancer in Africa was 0.30%. This review reiterates the fact that while breast cancer occurs in both genders, it remains rare in males. Thus, screening programs specific for males will not make economic sense, and thus particular attention must be paid to family history instead, Breast cancer in Africa is lower than the western world; however, both incidence and mortality rates are rising due to lifestyle changes, reproductive factors, and increased life expectancy and adaptation westernization lifestyle (47).The prevalence rate in African females living in Africa at 0.49% lower than high-income countries (11, 48) (47) (48). This may reflect a lack of awareness amongst Africans or a reduced exposure to risk factors. Of interest, the prevalence was highest in the south African region, thus pointing to the increased exposure to risk factors present in high-income countries.

Our findings highlight the paucity of data across the continent on one of the most critical cancers affecting women in most of the African countries and around the world. Almost half of the data for this review was provided by studies in North Africa. Central Africa was only represented by two studies (13,19). In addition to lacking active population-based cancer registries, most of the registries cover a small part of its population and do not meet high-quality registration standards (49) (50) (51). Adding to that, politically unstable countries, struggling with many other diseases and more concerning health issues causing a heavy load, compounds the difficulty in addressing the breast cancer burden (7).

When taking in the account of different settings between rural and urban areas; we have found more patients diagnosed with breast cancer in the urban areas, which could be explained by more awareness of female in these regions or because of easily accessible medical facilities in the major cities. On the other hand, prevalence rates in rural areas of Africa are fewer than the urban parts and fewer women in these regions seeking medical advice. Socio-cultural barriers could explain the lower prevalence rate and believes, lack of health care trained personnel, limitation of diagnostic facilities, and expensive treatment (18) (52) (53).

Our analysis of study design showed a lowered prevalence rate in retrospective studies, further emphasizing the need for well-designed prospective registries. Screening with mammograms is considered the gold standard for early breast cancer detection. Only six studies screened for breast cancer with mammography for women above the age of 40 years in three African countries (Tunisia, Egypt, and South Africa) reporting a combined prevalence rate of breast cancer of 0.63 (95% CI,0.46 to 0.82). These results, with only a small section of the population being covered, emphasize the need to implement population-based screening programs. Mammography screening for breast cancer has a sensitivity of 63 to 95%, and it is the only examination tool and considered the gold standard for early detection demonstrated to decrease in mortality rates in ages 50 years and above (54) (55). Its sensitivity increases with the presence of palpable lumps while the sensitivity decreases when

examining women with high dense breasts. Recent studies have been contributing the reduction of mortality rates in many developed countries to mammography screening programs (56).

In Africa, with its low income and weak health systems, population-based screening barely exists. Because breast cancer in African women develops at a young age, and because mammogram examinations are not performed before the age of forty years, an alternative cheap and available technique is used. Clinical breast examination (CBE) alongside breast ultrasound was used in most of our studies, giving a prevalence rate of 0.31%. Despite clinical breast examination only detecting tumors more than 2 cm in diameter, it remains useful to allow for treatment in the early stages (54) (55).

Strengths

Our systematic review is the first to calculate the prevalence of breast cancer in Africa.

One of the main strengths of this review is that we have systematically and vigorously performed the comprehensive search of multiple electronic databases using an African search filter. Furthermore, we have included all the data available with no language or time restriction to identify multiple publications. As suggested by the PRISMA guidelines statement, we have appraised the methodological quality of individual studies by using the standard quality assessment tools for calculation of the prevalence of breast cancer in Africa.

Limitations

Studies on early detection using screening of breast cancer are limited in the literature in most of the African regions. Of the included studies, there were only 12 countries from 54 which provided the prevalence rate for breast cancer in Africa. The remaining African countries have not been reporting any data on the prevalence of breast cancer nor have embarked on any screening for the population. Furthermore, the majority of the studies included in this systematic review used clinical breast examination for the screening of breast cancer as an alternative method, therefore, results of

prevalence rate can be underestimated because the screening purpose is to detect non-symptomatic lesions to prolong survival rates.

The large heterogeneity found amongst our studies was to be expected, as is often the case in prevalence meta-analyses with variation in study design. Exploring subgroup analyses did not alter the heterogeneity. The assessment of risk of bias showed low levels of risk and thus, we feel that the current study nevertheless provides the best estimates to date.

4.6 Conclusion

Studies that focus on the pattern of prevalence of breast cancer across Africa are limited. To our knowledge, this is the first study to address the prevalence of breast cancer on the African continent. Only 12 countries provided data for the calculation of the prevalence rate of breast cancer in Africa. Less than half of the African countries have active cancer registries; however, the quality and completeness of data are not equal to standard registries and only cover a small part of population groups. A massive effort and more resources are needed to address the burden of breast cancer in Africa, where incidence rates and mortality rates are increasing.

4.7 Recommendations

4.7.1 Implications for practice

We found that the prevalence of breast cancer studies in Africa is limited and the meta-analysis is low compared with high-income regions. However, the findings of this study will provide important baseline information for clinicians, health care workers, and policymakers regarding the burden of breast cancer in Africa.

4.7.2 Implication for research

This work serves to recommend prioritizing further research regarding the causes and methods of early diagnosis of breast cancer since it severely affects women at an early age. Because

mammography screening is not recommended to diagnose a breast lesion in young age groups, an alternative affordable method should be adopted in a low resource setting, and investment in cancer control is needed.

4.8 Ethics and Dissemination

This systematic review relied on secondary data that is accessible to the public and did not require formal ethical review [33]. The study protocol was reviewed and submitted to the University of Cape Town, Faculty of Health Science Human Research Ethics Committee with reference number (**HREC REF:561/2018**). The waiver is provided in the appendix.

4.9 Funding:

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4.11 Contributors

All authors conceived the study. MA, and LA contributed to the protocol and writing of the paper with support from DH and checked for relevant intellectual content. All authors agreed to the final version of the manuscript. The overall work was supervised by ME

4.12 Competing interests

None of the participating authors has a conflicting financial interest related to the work detailed in this manuscript.

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Appendix 4.5, Quality assessment criteria for Prevalence studies.

External validity

1.Was the study's target population a close representation of the national population in relation to relevant variables? (1 point)
2. Was the sampling frame a true or close representation of the target population? (1 point)
3. Was some form of random selection used to select the sample, OR was a census undertaken? (1 point)

4. Was the likelihood of nonresponse bias minimal? (1 point)

Total points (4 points)

Internal validity

1.Were data collected directly from the subjects (as opposed to a proxy)? (1 point)
2. Was an acceptable case definition used in the study? (1 point)
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability? (1 point)
4. Was the same mode of data collection used for all subjects? (1 point)
5. Was the length of the shortest prevalence period for the parameter of interest appropriate? (1 point)

6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? (1 point)

Total points (6 points)

Appendix4. 6, Checklist items.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	69
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	70
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	49
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	49
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	50
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	52
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	51
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	51
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	53
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	53
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	50
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	53
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	52
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	55

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	55
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	56
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	71
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	76
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	81
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	82 - 91
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	82 - 91
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	80
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	91 – 96
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	98
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	100
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	101
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	56

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix 4.7, Approval letter.

UNIVERSITY OF CAPE TOWN
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03 September 2018

HREC REF: 561/2018

A/Prof Mark Engel
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OMB

Dear A/Prof Engel

PROJECT TITLE: ESTABLISHMENT OF A BREAST CANCER REGISTRY FOR LIBYA (MS candidate - Ms M Owen)

Thank you for submitting your request to the Faculty of Health Sciences Human Research Ethic Committee.

The HREC note that the proposed study is a systematic review.

As the systematic review involves published literature available through publically accessible electronic databases, research ethics review and approval is not required.

This is in accordance with Section 1.1.8 of the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015), which states: *"Research that relies exclusively on publicly available information or accessible through legislation or regulation usually need not undergo formal ethics review. This does not mean that ethical considerations are irrelevant to the research."*

The HREC recommend that researchers refer to the PRISMA website, for the PRISMA statement and checklist, to facilitate the reporting of systematic reviews and meta-analyses. For more information, please refer to http://www.prisma-statement.org/.

Further, fundamental ethical principles for health-related research should be considered in the objectives and methods of the systematic review. See, for example, the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015)

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

CHAPTER FIVE

THE LIBYAN BREAST CANCER REGISTRY

5.1 Cancer registries

Cancer is a growing health problem causing high morbidity and mortality around the world. In 2018 there were an estimate of 18.1 million new cancer cases and 9.6 million deaths. Unfortunately, from the total cancer deaths, 70% were reported from low-and-middle-income countries (1) (2) (3) (4) (5) (6). Lack of basic health services, population growth, ageing, adaptation of an unhealthy lifestyle, and environmental changes contributes to a heavy cancer burden (1) (4) (5) (6) (7). Information such as number of cases, distribution, type of cancer, methods of diagnosis, cancer staging, the treatment used, and patient outcomes are fundamental in planning and monitoring cancer management programs (1) (6) (7) (8) (9). This information can be provided by comprehensive, well planned-out cancer registries although collecting this detailed information requires enormous staff effort, money, time, and continuation (9) (10) (11) (12) (13) (14).

5.1.1 Definition of cancer registries

A cancer registry is a type of disease registry, defined by the continuous, systematic collection, storing, summarizing and distribution of data on cancer occurrence and its detailed characteristics of patients living in a geographical area. A cancer registry is a long-term health information system useful for measuring the size of the problem and allows one to evaluate the performance and improve the management plans of public health approaches. The registry records patient details, which are available only for authorized individuals: therefore, patient confidentiality is assured; patients name and details will be displayed only as a code to the public (10) (11) (12) (13) (14) (15) (16) (17) (18).

5.1.2 Cancer registry aims

The primary purpose of such a registry is to provide an ongoing record of cancer cases for cancer researchers to detect the risks and causes of malignancies. Another important reason for the cancer

registry is to provide critical and accurate information to health officials in planning and evaluating cancer control and prevention programs (1) (3) (4) (10) (13).

5.1.3 Types of cancer registries

There are four types of cancer registries: hospital-based, population-based, pathology-based, and special purpose cancer registries (9) (17) (18) (19).

5.1.3.1 Hospital-based cancer registry

These registries are based on hospital records; cancer patient information in detailed; they are more commonly used than the population-based registry. The first hospital-based cancer registry was established in Connecticut, United States in 1926 to report cancer cases. They provide us with full detailed methods of diagnosis, treatment received, and the result of the treatment of a cancer patient. They usually report the number of cancer cases seen in the specific unit or hospital per year. These records will calculate the incidence of specific cancer compared to total cancer case admitted in the same hospital in a specific time. Therefore, the recorded information can be used instantly to provide future services needed in a given unit or hospital. Despite that, the occurrence and burden of cancer of the total population is not calculated. They usually limit sharing their information between hospitals; cases can be recorded multiple times in different hospitals, masking the actual cancer count in the community. Another essential drawback is that collected information may differ from health service to another; therefore, comparing findings may be difficult (10) (13) (17) (19).

5.1.3.2 Population-based cancer registry

"Population-based cancer registry data [are] an essential foundation of national cancer control planning – if you do not know your cancer burden, how can scarce resources be targeted at the most appropriate solutions for cancer?"

Dr Eduardo Cazap (Argentina), Past President, Union for International Cancer Control

The first functional population-based cancer registry was documented in Germany in 1926, although there have been many attempts through Europe before, these failed to accomplish their mission. There are more than 290 cancer registries around the world now, mainly in high-income countries. However, only a few covers the total population (5) (7) (8). From its name, they include all cases of cancer in the population over some time. These registries contain data collected from multiple sources, such as cancer centres, hospitals, private clinic, hospices, homes and shelters, pathology units, imaging centres, and death certificates registries. Population-cancer registries serve a more extensive range of services compare to other types of cancer registries. However, assessing and covering high-quality data when a large number of the population are involved can be difficult in continuing providing data (19).

These population-based cancer registries are exceptional resources for an epidemiologist; they provide the distribution of cancer in a selected population, which includes the incidence and prevalence. Another significant benefit from population-based cancer registry is the calculation of survival rates, which are useful in assessing advances in treatment. However, collected data can differ from one registry to another, causing difficulties in the comparison between groups of the population (15) (16) (17).

Cancer patients are followed for long periods until death, either due to cancer or other causes. These data are used for developing and supporting critical research, which could evaluate and assess control programs, screening methods, and its effectiveness for early detection of cancer lesions in reducing the mortality. However, population cancer registries require existing medical facilities and full cooperation medical staff in the community, which can require a long time and is costly.

An advantage in performing a population-based cancer registry, is that their data are vital to ensure health officials have accurate information to allocate funds, human resources and proper facilities. At the same time, they require support from regular and accurate census programs in parallel. This registry does not make sense unless the denominator of the population is available and able to identify nonresidents from

residential in the target population. Therefore, regional registries would be more effective in countries with larger population sizes (17) (18) (19).

5.1.3.3 Pathology-based cancer registry

In this type of registry, the data is collected from histologically diagnosed cancer, and they provide a quick cancer profile. However, the population from which the tumour tissues derived is not defined (10) (11) (17). Pathology based cancer registry can provide essential clues to determine the burden of cancer in a community. Nevertheless, they are prone to bias since they can underestimate cancer cases. However, in a low resource setting, this type of registry may be the only source in providing cancer information.

5.1.3.4 Special- purpose registry

This type of registry collects information on one type of cancer, for example, breast cancer or specific age group abnormality (17). They provide educational opportunities to learn more about a specific type of cancer and plan supportive measures for those affected in the population. Although they are very rich in detailed cancer information, these type registries are not typical, and only a few have been established.

In conclusion, all types of cancer registries are of great value for individual and community health care. Together they provide us with the complete picture of all the essential information that is related to plan, evaluate, and control cancer burden.

5.2 African cancer registries

The cancer burden is increasing in Africa, require urgent initiation and functioning high-quality population-based cancer registry systems to provide evidence-based cancer control program. At the moment, only a few have been selected to submit their data. In Africa, there are eight countries: Algeria Egypt, Libya, Tunisia, Malawi, South Africa, Uganda, and Zimbabwe, report an annual high-quality incidence data; however, only four provide mortality statistics in Africa (9).

The African Cancer Registry Network (ACRN) has launched on the first of March in 2012, partnered with the International Agency for Research Cancer (IARC) to improve cancer surveillance in the Sub-Saharan region. More than 20 countries registered from the Sub-Saharan region and started providing data capable of assessing control measures. In contrast, 19 countries from Africa have no incidence or mortality cancer data (5) (11) (18).

5.2.1 The Benghazi, Libya cancer registry

The Benghazi cancer registry was established in 2002 and provide cancer incidence from eastern Libya, covering 28% of the total population. This registry, as most of the African country registries, partnered with IARC. The result from this registry showed that the pattern of the incidence of many cancers differs from estimated figures based on neighbouring countries data. The registry provides an annual report of cancer incidence and important trends are available to the department of health. The presentation of data can initiate cancer research projects in the coming future to overcome cancer burden (18, 20).

5.3 The Libyan breast cancer registry

5.3.1 Introduction

There were 2.1 million new diagnosed females with breast cancer in the year 2018. Breast cancer has become the most frequently diagnosed cancer around the world and contributing about 25.4% of all total new cancer cases in women. The highest recorded incidence rates were from Australia/ New Zealand, most of Europe and North America. This cancer has caused over a half million deaths in both sexes, the highest country reporting the most mortality rates from breast cancer was Fiji in 2018 (1). Unfortunately, the majority of deaths from breast cancer occurred in both middle and low-income countries, with women diagnosed at a late stage and early age, with a lack of awareness and poor early detection plans, therefore, the survival rate is low (1) (21) (22) (23) (24).The lowest recorded five-year survival rates were in the Gambia, Western African region, in which only 12% of women survive the five years after diagnosis with breast cancer (25) (26).

On the other hand, females living in the high-income countries have a prolonged five-year survival rates that reaches more than 85-90% in certain countries, particularly French, Danish, and Japanese women. While in North American and Canadian women, 85% survive ten years after diagnosis of a localized cancer lesion that has not spread beyond the breast tissue (1). This prolongation of survival rate in high-income countries can be explained by the availability of both awareness and early detection screening programs — also, the availability of a variety of cancer medication and availability of cancer rehabilitation centers (1) (27) (28) (29).

Both men and women can get the disease; however, breast cancer in males is quite rare, accounting for less than 1% of all breast cancer around the world (30) (31) (32) (33) (34). The male to female ratio is 1: 100 in the United States and Denmark, while in Sub-Saharan Africa report from a large meta-analysis showed a high male to female ratio 1:14 (1) (30) (35). The risk factors associated with developing breast cancer in males are similar to females in that they increase with age and having a family member with the disease. However, the average age is around a decade older than in females. Outcomes of male breast cancer are reportedly worse than females, however, because of lacking extensive population studies, the rarity of the disease and missing complete data, management plans regarding breast cancer are unclear for males diagnosed with breast cancer (33) (34).

In Africa, due to rise in population numbers and life expectancy, exposure to risk factors and weak health care system is associated with a rise in cancer incidence rates (22) (23). The incidence of breast cancer in Africa from population-based registries was ranging from 29.3% in North Africa, and 22.4% from Sub-Sub-Saharan region (35). Although the African continent is a mixture of multiple ethnicity, women share the same characteristic in poor outcome after developing breast cancer. African women develop breast cancer at an early age, and they present at a late stage, resulting in limiting treatment options and causing

more exposure to toxins from anti-cancer treatment leading to an increasing of both morbidity and mortality (19) (21) (23).

Libya is the fourth largest African country located in North of Africa on the southern shore of the Mediterranean Sea. With a population of 6,278,000 (2006) Libya is one of the lowest population density countries in the world and labelled as one of the upper-middle-class income countries in Africa. However, despite being a wealthy country, Libya is facing severe health care problems. Nowadays, many Libyans are adopting unhealthy lifestyles such as consuming more fatty food, less fibre, less physical activity, smoking tobacco, and drinking alcohol. This change in lifestyle together with environmental changes and high life expectancy are perhaps the causes in rising cancer rates. Primary cancer prevention programs such as tobacco control, alcohol control, obesity prevention, and promotion physical activity are minimal to non-existent (20) (29) (30). Lacking training persons in all health divisions, inactive public awareness programs, no screening methods implemented, weak health departments, continuous instability of government and carelessness of patient are all part of the enormous struggles facing Libya today.

There are two national cancer institutes and three oncology and haematology departments in Libya; unfortunately, they are only distributed in the Northern part of the country in the major cities. Even though these centres cover the majority of the Libyan population, the remaining rural areas are not reachable. These centers provide full cancer facilities such as radiation units, diagnostic pathology laboratories, surgical theatres but only one positron emission tomography scanner for the total population is available.

Despite the free healthcare in Libya, cancer remains a low priority, and patients seek medical advice at a late stage, as observed in many regions in Africa. In addition, because of Libya's conservative society, several social and cultural factors affect those seeking western medication and prefer alternative medicine

(36) (37) (38). This pattern of seeking medical support at a late stage minimizes the treatment options for clinicians in controlling cancer and results in more aggressive radical surgery rather than primary lesion removal, and increased exposure to more toxins from receiving anti-cancer treatment for metastatic lesions ; together these results in a rise in both morbidity and mortality rates (35, 39).

In 2002 the first population-based cancer registry published its data from Benghazi Medical Center reveals that the most common cancer among Libyan females was breast cancer. However, these results were only covering 28% of the total population. Results from the population cancer registry reported that breast cancer represents 26 % of all cancer types (39) (40). The latest incidence rates of female breast cancer were 23.2 %, breast cancer caused a total of 15% of all cancer-related deaths in females (18). Meanwhile, hospital-based cancer registries have revealed that breast cancer new cases had increased slightly in 2018. The results of breast cancer incidence in females are 23.8% for all ages and caused 14.9% mortalities in the same year (41) (42) (43) (44).

Breast cancer is more prevalent in younger age groups with a median age of 44 years, mainly during the pre-menopause period around ten years younger than in high-income countries and similar to most of the African region (18) (41) (42) (43) (44). In contrast, the mean age group in males is 61 years; as previously mentioned men are usually seen at medical facilities only in an advanced stage. The overall five-year survival rates are 57% for men compared to females 78%, which is more than most parts of Africa (25) (40) (41) (42) (43) (44).

In Libya, the management plans are similar and updated according to the national cancer management plans. Breast cancer is managed by a multidisciplinary team that consists of a surgical oncologist, medical oncologist, and radiotherapist. The team discusses each patient separately, and a management plan offered to the patient. This plan includes considering the health status of the patient and stage of the disease. However, cancer medications, permanent oncologists and palliative care centers may not be available.

Furthermore, many patients travel abroad to seek medical care elsewhere hence records lost from the health system.

Proper surveillance programs are mandatory to monitor cancer trends; high-quality record-keeping and evaluation of methods of early diagnosis in high-risk groups are crucial to upgrade management plans. More attention and effort should take place in improving patient awareness programs, starting in small community villages and expand through the country. Education of risk factors causing cancers and explanation of early symptoms and signs and its importance in early seeking medical advice are mandatory. Training medical health persons for cancer diagnosis and early referrals can improve the quality of life of cancer patients. Together with updating of advanced diagnostic techniques, providing cancer treatment drugs, all together to improve patient quality living and rise in healthcare in Libya.

5.4 Libyan Breast cancer report Form

5.4.1 Aims:

A breast cancer registry is a special purpose registry that collects exhaustive, detailed information from patients diagnosed with breast cancer. The main aim of developing a Libyan breast cancer registry is to provide an opportunity to learn more about the disease development, the changes through the course of the patient's life and outcomes that serve as an information resource for cancer research. Secondly, we will be able to track the incidence, mortality and survival of patients diagnosed with breast cancer and their distribution in Libya. Finally, the information will be translated into figures to help plan supportive measures and control to those effected and at high risk for improving breast health care in Libya.

5.4.2 Designing the form:

We have collected a comprehensive set of information for breast cancer. Information relevant to breast cancer was summarized into simple questions that can be answered by both the registry team and the patient. These information's are useful to show whether performing the usual screening programs or the existing methods and prevention attempts are making a difference for cancer control.

5.4.3 Content of the Libyan Breast Cancer Registry Form:

5.4.3.1 Manual of operations

The manual of operations intends to guide the registry team to identify and record results specific for breast cancer patients. In this section, there is a full explanation of how to answer and fill in the questions. Examples answered, and details of contacts are included in the manual in case of any clarity is required. (Appendix 1 LBCR 7, page 5)

5.4.3.2 The forms

There are three parts for the registry form I, II, AND III.

I- This part consists of demographic data and cancer information. The main detail consists of patient personal data which consists of patients' medical history, general examination, breast examination, methods and results of the diagnosis, and the treatment offered. (Appendix 1 LBCR 9.2, page 21-37)

II- Follow up sheet that used for continuous follow-up _ each time the patient is advised to visit a new follow up form is completed. All new information regarding patients' details, new complaints and investigation findings and any changes or treatment offered at the visit, are recorded in this section. (Appendix 1 LBCR 9.2, page 38-44)

III- Death information sheet, details of deceased recorded accompanied with a copy of the actual death certificate, and an autopsy report in case it was required. (Appendix 1 LBCR 9.2, page 45-46)

5.4.3.3 Appendices

Additionally, to the above, the appendices will contain the consent form in both English and Arabic languages, the international occupation list, BIRADS table for mammography readings, cytology table for fine needle aspiration results, and TNM classification.

5.5 Reporting

The registry team will be provided with a working space with the required equipment and facilities to ensure following the correct procedures in the registry. Furthermore, the registry team will be trained and updated regularly to secure the reporting system is parallel with the international registry. A budget will be placed to guarantee the continuation of the registration of the team members and no missing of patients recording or dropping periods (9) (10) (11).

At the start, printed copies will be distributed between registry teams for practice, calculate the required time needed to fill in the forms, and piloting to ensure no missing information, and ready for the electronic version. The printed copies will guarantee a backup in case of no electronic documentation available for any reason, such as a shortage of electric power or destruction of files. However, this method will consume team members' time to complete, and duplications of patients are frequent with this type of documentation. Besides, paper documents require more office space to be stored, misplaced, lost, and are risk of exposing patients' privacy. Furthermore, accessing copies is difficult from other places without physically going to the location (11) (12).

An electronic capturing of patients' information will be placed and activated at the same time printed copies are filled, to ensure smooth patient recording. As soon as the process familiar with the registry team, electronic data recording will take over. Electronic forms filling will save time for team members. The correction of electronic forms mistakes without the need for repeating another copy, changes are made fast and can be saved instantly. Also, the duplication of patients avoided because the data stored for

the same patient will appear immediately. Furthermore, registry files can be duplicated and stored easily to ensure backup data prevent loss or file corruption. Besides, effortlessly sending reports between the registry team, saving time and money (13) (14) (15) (17).

5.6 Objectives :

Each part of the LBCR will be addressing the following objectives:

LBCR Form I: Baseline form

- To describe the demographic characteristics and presenting features of Libyan breast cancer patients.
- To compare disease occurrence in different groups and by regions within the country.
- To list details of known and possible related risk factors such as family history, type of food used, occupation of patients and associated medical problems.
- To describe available screening methods used and to measure how effective these are in the early detection of breast cancer.
- To measure the common tumors types diagnosed and their specific characteristics of Libyan breast cancer patients.
- To stage disease presentation, time of diagnosis of patients, and timing of seeking management care.
- To monitor guidelines followed in the management plan from the investigation, procedures, and treatments used locally for both early and advanced breast cancer patients.

Form II LBCR: Follow-up form

- To determine the recurrence rate and cancer status of breast cancer patients.
- To determine the effect of treatment used and related complications.
- To describe the different stages of five-year and ten-year survival of patients after diagnosed with breast cancer.
- To determine the development of new types of breast and other cancer.

Form III LBCR: Deceased form

- To quantify the annual breast cancer mortality rate.
- To determine the age of death with breast cancer.
- To determine the regional distribution of morbidity and mortality rates in the country.

5.7 The implication of the LBCR registry:

Implications for the clinical practice:

- This registry will to serve as a notification and reporting system used for breast cancer incidence, prevalence, and trends through appropriately designed studies that will be generalizable to the whole population of Libya.
- We hope to empower breast cancer patients through information and data on breast cancer treatments in Libya
- This registry will assist medical professionals to generate reports tailored to guide and improve outcomes of Libyan breast cancer patients.
- To set a model for other cancer registries to guide other cancer control plans in Libya.

Implications for future research:

- Identify key areas that could be targeted to improve outcomes.

- Data within registries provide an ideal platform for new research and policy initiatives to improve the quality of health systems in Libya.
- Further research should be strongly encouraged for simple and effective tools for early breast cancer screening.
- Collaborate with other research agencies/institutions on breast cancer studies.

Implications for policy Advocacy:

- Highlight primary preventive measures related to available risk factors in developing breast cancer.
- Suggest secondary preventive measures in designing better breast cancer early detection methods specific for high-risk populations and early age groups.
- Advocate for awareness campaign programs and support patients diagnosed with breast cancer through there life journey.
- Collaborate with national and international organizations to help improve breast cancer care in Libya.
- Influence decision-makers to set priorities and not to waste precious resources to overcome breast cancer in Libya.

5.8 Conclusion:

The clinical picture of breast cancer in Libya differs from Western countries due to the high proportion of patients develop the disease at a younger age and seek management care at an advanced stage. The Libyan breast cancer registry is the initial step to provide all the essential information that is related to plan, evaluate, and control breast cancer burden.

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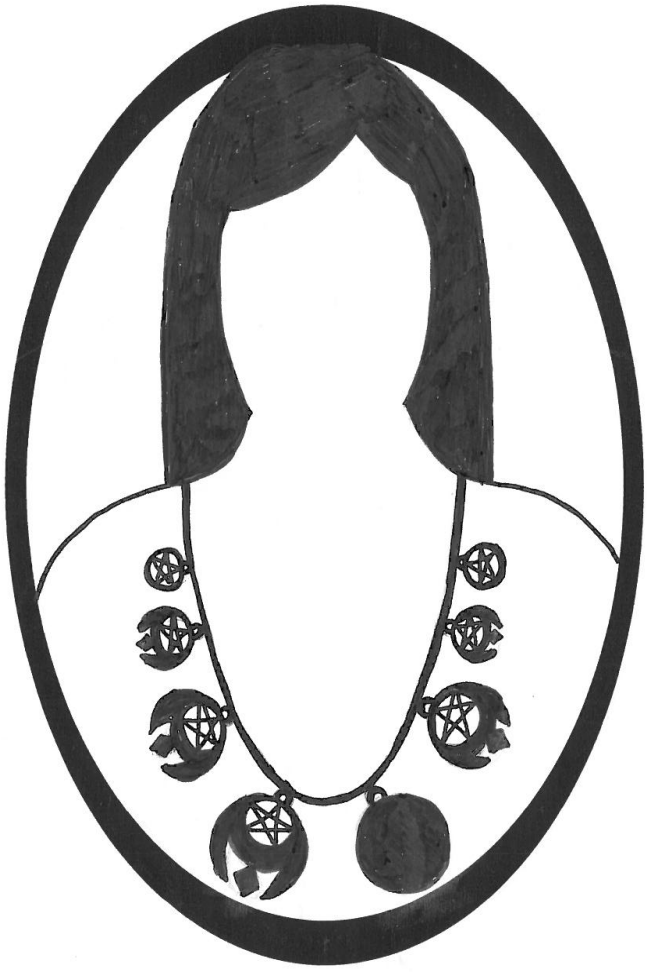
LIBYAN BREAST CANCER REGISTRY FORM.

(LBCRF)



Muna A O Abulkasim

2. CONTENTS OF THE LIBYAN BREAST CANCER REGISTRY FORM

3. ABBREVIATIONS

- ALND = Axillary lymph node dissection.
- BI-RADS = Breast Imaging Reporting and Data System
- BMI = Body mass index.
- BRCA 1/2 = Breast cancer gene 1 and Breast cancer gene 2.
- BCS = Breast conserving surgery.
- C50 = Breast cancer code ICD
- BSE= Breast self-examination.
- CBE= Clinical breast examination
- cm = Centimeter.
  CT scan = Computed tomography
- C = Cytology diagnosis based on microscopic examination of cells.
- DCIS = Ductal Carcinoma In Situ.
- ER = Estrogen receptor.
- FNA= Fine Needle Aspiration.
- G = Gravida (total number of confirmed pregnancies regardless of the outcome of the pregnancy)
- HRT = Hormonal Replacement Therapy.
- HER2 = Human Epidermal Growth Receptor 2.
- ICD = International Classification of Diseases
- ILC = Invasive Lobular Carcinoma.
- IDC = Invasive Ductal Carcinoma.
- In Situ = Cancer cells not progressed through the basement membrane.
- Kg = Kilogram.
- LBCR = Libyan Breast Cancer Registry.
- LBCRF = Libyan Breast Cancer Registry Form.
- LCIS = Lobular Carcinoma In Situ.
- LN = Lymph Nodes.
- MRI = Magnetic resonance imaging.
- mm = millimeters.
- mmHg = millimeter mercury.
- -ve = Negative.
- P = Parity (number of pregnancies a woman has given birth to alive or lost, fetus more than 20 more than weeks)
- PET scan = Positron Emission Tomography
- PR = Progesterone receptor
- +ve = Positive.
- RSA = Republic of South Africa.
- SLN = Sentinel lymph nodes.
- SLNB = Sentinel lymph node biopsy.
- TNM / T=Extent of the tumor, N=Regional lymph node metastasis, M=Distant metastasis.
- U/S = Ultrasound.
- X-ray = Radiological diagnosis based on x-ray scan.

4. INCLUSION CRITERIA

All criteria must be present:

- Participation must sign a consent form.
- A histopathology report must make the diagnosis of breast cancer.
- Registry for both male and females' participants diagnosed with breast cancer.
- All age groups diagnosed with breast cancer included in this registry.

5. EXCLUSION CRITERIA

Do not proceed for registration if:

- No consent forms.
- Diagnosis without a histopathology report.
- Primary cancer is not breast cancer.

INFORMED CONSENT

- Written informed consent must be obtained before enrolling participation (A template informed consent included in the appendices in both English and Arabic languages S4A, S4B).
- If the participant cannot read or write, a thumbprint will be sufficient, and a witness must be present to sign the form.

6. PATIENT CONFIDENTIALITY

Participant personal data kept away from the public; the participant name will be de-identified. Data will be key coded. The forms will be locked in a secured place accessed only by the registration team members. Any required information about the registry form participant can contact the registry staff. Details of contact names and cell phone numbers of LBCR coordinators will be in section 9 of the manual of operation.

7. MANUAL OF ANSWERING THE FORM

7.1. General information to be followed to complete the registry form:

- For the person filling in the form: Please read the manual carefully and follow the instruction for each section.
- Forms must be filled correctly; please take time to fill the form as all details that are asked are crucial, and this information will be used in an attempt to help a patient suffering from breast cancer.
- Forms must be completed with a black colored pen, NOT with a pencil or any other color, please fill the form by writing from left to right in the English section and from right to left in the Arabic section.
- Ensure that the participant meets the eligibility criteria and exclusion criteria not applied.
- If a consent form is not filled and signed by the participant/family member, please do not proceed.
- The participant or relative responsible for providing any required information must sign and record his/her document.
- If the participant cannot write or read, then relative details must be filled in the given section, his/her signature, address, and telephone numbers must be documented for any further information.

- If the participant is given a verbal consent and cannot write a fingerprint of the participant will be sufficient; if the fingerprint is not applicable, witness details should be present to confirm a verbal consent.
- After the consent form completed, start filling all the pages and follow the instruction of each question carefully.
- Please make sure that all pages available, numbered in a sequence, and fill accordingly. This part of the information is critical for data quality. Each page must be filled and checked for all sections. Please take the time to complete the diagrams of both breasts by drawing the site of tumor and lymph nodes or any other findings. Complete the family pedigree by using the available codes in the same sections; look at the examples provided in the given sections.
- In case of any changes on the form, only cross the previous information without writing on the crossed site. Write the initial of the person, corrected the information, and fill in the date in the given space or comments. Do not use correction fluid.
- There will be a space to comment or to add an essential message for each question. Please write neatly and legibly in the given space.
- If the participant does not complete the follow-up, an attempt via telephone must be made to remind the participant for the date of follow-up, and all notes must be documented. If the participant does not respond, a family member of the participant will be contacted for completing missing data.
- Please update all-new details of the participant and the new details of the person responsible for filling the form for each visit.
- When question heading does not indicate more than one answer, only mark one answer.
- The person filing the form initial: the first letter of his/her name in the first box, the middle name first letter in the second box, and the last name first letter in the third box, as shown below.
- The initials are repeated on each page with participant ID, e.g. (Name of the doctor filling the form is: Ahmad Nori Abdulsalam).

|_A_|_N_|_A_|

- If the person does not have a middle name, place a **(-)** in the middlebox, as shown. (Name of the doctor filling the form is: Khalid Daw).

  |_K_|_-_|_D_|

- In the giving boxes, please mark the specific answer with an X in the box instead of ✓

  e.g., (The participant is a Male).

  |_X_| Male

  |_ _| Female

  And Not, e.g. (The participant is a Male).

  |_√|Male

  |__| Female

- When writing the date, start filling from left to right, the first two digits are the days of the month, the second two for the month in numbers, and the last four digits for the year: Please write above the light letters DD /MM /YYYY.

  e.g. (Date of birth of participant is on the third of February 1976).

  Date of Birth: 03 /02 /1976.

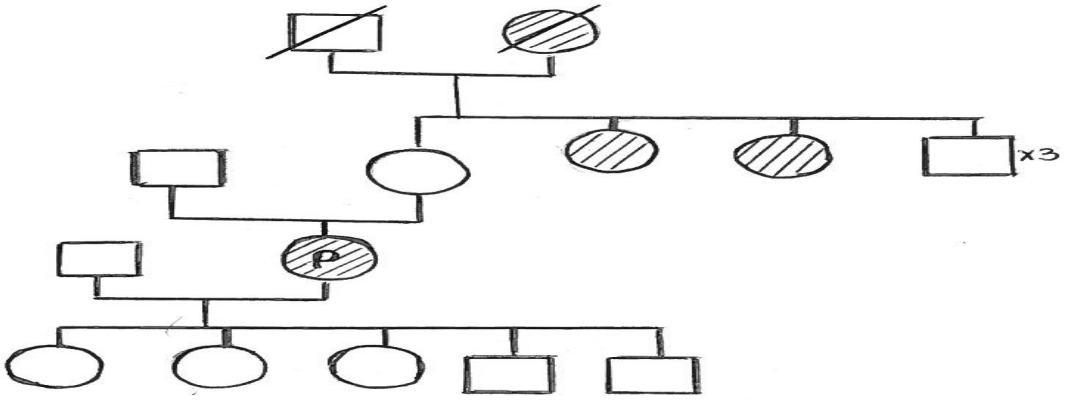
- In case the answer is two digits, and there are three boxes available, fill the first number with zero.

  e.g. (If the patient's pulse rate is 79 beats/ min fill the boxes as shown).

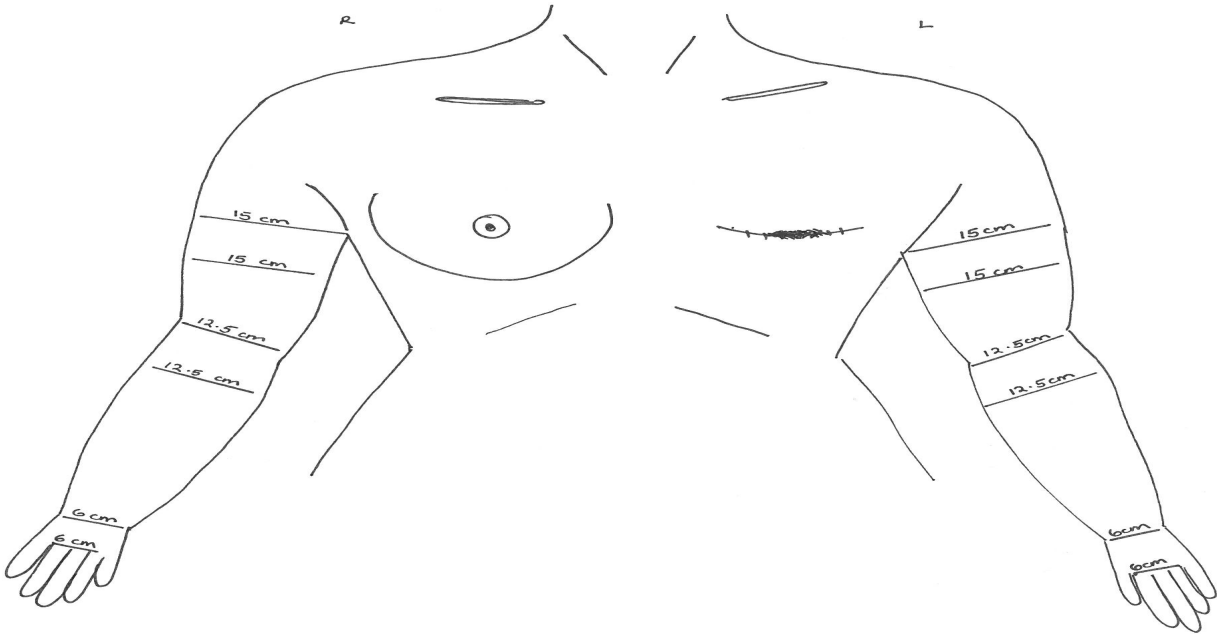
  |_0_|_7_|_9_| beats/min.

- Please take the time to fill the diagrams provided in each form and measure the required parts when needed.
- For the family pedigree, use the provided codes and fill accordingly. The P is for the Participant: if the participant is a male, draw a square around the [P]. If the participant is a female, draw a circle around the Ⓟ. Family members with positive breast cancer must be placed in the diagram to indicate the relation to the participant, and please indicate the sex of relative with positive cancer.

e.g. (A 50-year- old female participant diagnosed with breast cancer has three daughters and three sons. Had a maternal grandmother who died with the same disease and two of her daughters are receiving chemotherapy for breast cancer in the oncology unit).



- In the breast cancer diagram, draw the lesion the participant had before any procedure in the LBCR(i). Indicate the site of lesions, any changes or findings such as scars, new lesions in each visit in the LBCR form (ii). Please do not forget the measurements of both upper limbs for each visit. e.g., A female participant diagnosed with left side breast cancer operated with a left mastectomy and ALND one year back. She came with a thickening at scar site for further management.



8. CONTENTS OF EACH SECTION

- **The LBCR manual of operation** that explains how the required data are collected. It also contains all the required tables to answer any detailed information regarding breast cancer. The appendices of LBCR contain the consent form in both languages English and Arabic. Furthermore, the contact information of staff members will be available for any clarity, comments, and advice.
- **LBCR (i),** this part focuses on all the details of the participant personal information, personal history, family history, method of diagnosis, and treatment received.
- **LBCR (ii)** is the follow-up form, condition of the patient asked, any new complaint, any change of management plan is all included in this part of the registry. For each visit, a new form filled with newly updated data for the participant.
- **LBCR (iii)** contains the deceased form, when the participant passes the information will either be collected from hospital files, the doctor in charge or family member.

8.I LBCR(I)

- This part consists of **17** pages; each page contains the page number from **1-17**, the participant's **ID, ICD** code for breast cancer **C50**, and the doctor filling the form initials. The questions divided into 21 sections from **A-U**; each section has subtitles, and space is provided to fill-in the answers.
- **Section A**: The registry members give the participant ID case in a sequencing method. If the participant has another primary breast cancer should be cleared and documented in the given space.
- **Section B**: The person filing the form details must be included, in case of any missing data or any clarity needed can be solved by contacting him/her.
- **Section C**: Participant reliable relative full name, relation, and cell phone number are asked and filled in the given space. The relative contacted in case the participant has missed a visit, or the

participant has lost contact. Also, if a participant cannot read or write, a relative can sign the consent form after the patient's verbal permission.

- **Section D**: consist of question-related to the full participant name, address, age, date of birth, country of birth, and marital status. Nationality of the participant included, and more details asked for Libyan patients. Religion, level of education, and type of occupation asked. The type of occupation filled from the national occupation classification table in the appendices (T1).
- **Section E**: This part of the form is asking details regarding participant personal habits. Details such as: if the participant smokes, drinks alcohol, and sleeping routines. The last section on this page is asking about the type of food; the participant is taken food that is common in the Libyan culture on a daily basis. The amount of food suggested is roughly measured and found on the same table.
- **Section F (i):** This section can have multiple answers to choose from if the participant is known for any medical diseases, the age the medical condition started, is the participant taken regular medication all must be filled. Finally, space provided for any changes that happened or any comments.
- **Section F (ii):** In this part of the registry, we are asking about any procedure/ operation the participant had, also if the participant had a history of cancer type and treatment that he/she received.Document any past trauma to the chest wall.
- **Section G (i):** This section is asking for any family history of cancer, especially breast and ovarian cancer. We also like to understand if any genetic counseling was done in cases of positive breast/ ovarian cancer.
- **Section G (ii):** The family pedigree in this section can be filled by using the provided codes. The dotted lines can be filled if the extended family is known. (an explanation was done on page 7)
- **Section H**: This section both of parts (H i and H ii) are only to be answered for the female participant. This section questions related to hormonal changes the female participant goes through, the age of menarche, menopause, and pregnancy period. We also would like to collect information regarding the uses of any hormonal treatment (contraceptive or HRT) through life.

- **Section I**: This section we are asking if the participant ever had a regular checkup for the screening of breast cancer. The results of the mammogram BIRDS table are in the appendices of manual of operation of the LBCR on page 16, the doctor filling in the form can check reports and circle finding accordingly.

  e.g., If the participant has a regular checkup, the last mammogram reported:

  The finding is benign breast lesions, and there is no cancer appearance in the images of both breasts circle (II) for each site of the breasts.

  (L) 0 I (II) III IV V VI Date: 19/ 07/ 2010.

  (R) 0 I (II) III IV V VI Date: 19/ 07/ 2010.

- **Section J**: Start taking information regarding the current breast cancer the participant was registered. The symptoms the participant had, the method of diagnosis.
- **Section K**: Vital signs of the participant, also record the height and weight to calculate BMI.
- **Section L**: Fill in the picture of the site of breast lesion diagnosed with breast cancer please indicate the site and lymph nodes if they were palpable. If there are any other scars or anomalies, please draw and indicate on the same picture. Please take time measuring all required sites of both upper limbs and fill in the measurement in centimeters. An explanation was provided on page 8
- **Section M**: In this section, the participant will be sent to the breast cancer committee to decide the management plan. The full participant laboratory, histopathology staging, and metastasis work up are discussed with the surgical, radiologist, a medical oncologist. Please fill in the committee decision in the given space, type of plan the participant will receive. On page 17, the TNM classification can be checked.

- **Section N**: This section asks questions regarding the surgical procedure performed on the participant after diagnosis as part of the breast cancer management plan. The details of pathological staging must be filled from page 17.

- **Section O**: As part of the participant work up this section includes the laboratory investigation, please fill in the last results of the participant workup before committee discussion
- **Section P**: This section will be a continuation of participants work up for metastasis. Please fill in the given space of all types of scans and radiology tests performed
- **Section Q**: This section of the ninth page collects information of the chemotherapy regime, the type of drugs received, the number of cycles advised, dates of both start and finishing chemotherapy.

- **Section R**: This section will collect information regarding if the participant has received radiotherapy, the type of radiation the dose, and the site: document both starting and ending dates of treatment.

- **Section S**: This section consists of the type of hormonal and target therapy offered to the participant. Please write the type of drug used, dose, the route given, started date, and when it was stopped.

- **Section T**: If the participant taking any other medications not part of breast cancer management please document the type of medication. Also, if the participant is registered in a trial provide the name of trail.
- **Section U**: This last section is for any comments or changes of information. The person performing this change initials, and date should be documented.

8.II LBCR(II) FOLLOW-UP FORM

- This part of LBCRF (ii) consists of seven pages.
- The date of each visit must be filled, participant ID, code of ICD of breast cancer, and initials of person completing the form must be recorded for each visit.
- Fill in the number of visit box specific for each visit.

  e.g., This is the third visit for the participant, fill the number 003 in the box.

  The number of visits:

  |_0_|_0_|_3_|
- If the participant missed a visit, please indicate the reason and record the method of contact.
- If the participant refused to continue, please indicate the date.
- If after family members or hospital record indicates the participant has passed fill in the **LBCR (iii).**
- Any changes in personal history, change location, new medical conditions, new imaging, laboratory results, or new procedures must be documented and updated.
- Examination of participants' general appearance, site of previous primary cancer, and if there are any new changes must be added to provided space and drawn on the given picture.
- Please measure both the upper limbs of the participant in each visit.
- For the female participant, ask the age of menopause if the participant had a regular cycle at the time of diagnosis.
- For female participant document if new pregnancies or procedure offered after starting cancer management.

8.II LBCR (III)

This part of the Libyan Breast Cancer Registry **LBCR (iii)** consists of two pages and has three sections.

- Make sure the **ICD** specific for breast cancer, the **ID** of participant matching his information. Also, clarify if the participant is registered for more than one primary.

- The first section deceased details must be filled correctly from the hospital file; details from another source must be specified.
- Fill in the date of death and age of deceased in the second section and his/her status of the last
- contact from the **LBCR (ii)**/ Hospital files.
- State the last results of an examination of the participant before death by choosing the appropriate disease status in section C.
- If participant died due to other causes other than cancer secondaries or medication is taken for breast cancer, please specify.
- A copy of the death certificate should be available.
- State if there is any new information recorded, place of death, and autopsy reports.
- If an autopsy was performed, fill-in the result and date.

9. APPENDICES

This part of the breast cancer registry consists the tables, the forms, the consent forms, and project coordinators.

9.1 TABLES

9.1.1 Table T1: International standard classification of occupation

Group 1: Legislators, senior officials and Managers. Legislators and senior officials' Corporate managers. General managers, Businessman	**Group 7**: Craft and related trade workers Extraction and building trade workers, Metal machinery and related trade workers, Precision hand craft and printing and related trades workers, Other craft and related trade workers
Group 2: Professionals Physical, mathematical and engineering science associate professionals/ technicians, Teaching professionals, Other professionals.	**Group 8**: Plant and machine operators and assemblers Stationary plant and related operators Machine operators and assemblers, Drivers and mobile plant operators
Group 3: Technicians and associate professionals Physical, mathematical and engineering science associate professionals/ technicians, Life science and health associate professionals/ technicians. Teaching associated professionals/technicians. Other associated professionals/ technicians	**Group 9**: Elementary occupations Sales and service elementary occupations Agricultural fisheries and related laboureres Laboureres in mining and construction manufactural and transport.
Group 4: Clerks Clerks, Customer service clerks	Group 10: Armed forces Armed forces
Group 5: Service workers and shop and market sales workers Personal and protective services workers Models, salespersons and demonstrators	**Group 11**: Homemaker Housewife/Househusband A women or a man who manage her/ his own household as his/her main occupation not merely an unemployed person. Need not necessarily be married
Group 6: Skilled agricultural and fishery workers Market-oriented skilled agricultural and fishery workers, Subsistence agricultural and fishery workers.	**Group 12**: Student Anyone engaged in school / collage / tertiary level activity.

9.1.2 Table T2: BIRDS classifications table

BI-RADS I	This score means an additional imaging is needed/ or incomplete image
BI-RADS II	This score results are negative for any signs of cancer
BI-RADS III	The finding are benign breast lesions and there is no cancer appearance in the images
BI-RADS IV	This score findings are suspicious lesions can be either: a- low suspicious for malignancy. b- moderate suspicious for malignancy. c- high suspicious for malignancy
BI-RADS V	The finding is highly suggestive of malignancy and around 95% chance of breast cancer
BI-RADS VI	The radiologist has already the diagnosis confirmed of malignancy.

9.1.3 Table T3: Cytology FNA classification

Code	**Microscopic findings**
C1	inadequate/ insufficient/ not-representative
C2	Benign cells/ no evidence of malignancy
C3	atypia/ indeterminate
C4	suspicious of malignancy
C5	malignant cells

9.1.4 Table T4: TNM clinical and pathological classification, (Breast Cancer TNM anatomical stage groups AJCC UICC 8th Edition). / Staging of breast cancer based on TNM.

T = Tumor, N= node status, Pathological (pN) / Clinical status (cN), M = metastasis, and cancer staging.

Tumor	
Tx	unable to assess primary tumor
T0	no primary tumor detected
Tix	type of primary tumor is carcinoma in situ, Tis (DCIS) = Ductal carcinoma in situ. OR Tis (Paget) = only the nipple without invasive carcinoma or DCIS lumps of the breast.
T1	the size of tumor is not more than 20mm in greatest dimension.
T1mi	tumor size ≤1 mm in greatest dimension.
T1a	Tumor size >1 mm and less than 5 mm in greatest dimension
T1b	Tumor size >5 mm and less than 10 mm in greatest dimension
T1c	Tumor size more than 10 mm and not more than 20 mm in greatest dimension.
T2	Tumor size more than 20 mm and not more than 50 mm in greatest dimension
T3	Tumor size more than 50 mm in greatest dimension.
T4	Tumor of any size with direct extension to the chest wall, with or without skin ulceration or macroscopic skin nodules.
T4a	Extension to chest wall, only include pectorals muscle without adherence or invasion to chest wall.
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema including pea u d' orange of the skin
T4c	Both T4a and T4b tumor.
T4d	Inflammatory carcinoma type breast cancer

cNx	Regional lymph nodes cannot be assessed, in case of previously removed by surgery.
cN0	No regional lymph node metastases can be detected neither by clinical examination nor by imaging.
cN1	Metastasis of tumor to the ipsilateral level I, II axillary lymph nodes, lymph nodes are mobile not fixed.
cN1m	cN1mi – Micro metastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm, in cases where sentinel node biopsy is performed before surgery
cN2	cN2 – Metastasis of tumor to ipsilateral level I, II axillary lymph nodes. The lymph nodes are clinically fixed or matted. Also, when metastasis of tumor to the ipsilateral internal mammary nodes when clinically no evident of axillary node metastases at same side.
cN2a	Metastasis of tumor to ipsilateral level I, II axillary lymph nodes. The nodes are either fixed to one another or to other surrounding structures.
cN2b	Metastasis of tumor cells to ipsilateral internal mammary nodes, and in the absence of axillary node metastases clinically.
cN3a	Metastasis of tumor to ipsilateral infra-clavicular lymph nodes.
cN3b	Metastasis of tumor cells to ipsilateral internal mammary with clinical axillary lymph nodes involvement.
cN3c	Metastasis of tumor cells to ipsilateral supra clavicular lymph nodes with or without axillary or internal mammary lymph nodes.

pNX	Regional lymph nodes cannot be assessed (eg, previously removed, or not removed for pathologic study).
pN0	No regional lymph node metastasis identified or isolated tumor cells (ITCs) only.
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by hematoxylin and eosin stain [H&E] or immunohistochemistry [IHC]
pN0(mol +)	Positive molecular findings (reverse transcription polymerase chain reaction [RT-PCR]), but no regional lymph node metastases detected by histology or IHC.
pN1	Micro-metastases, or metastases in one to three axillary lymph nodes, and/or clinically negative internal mammary nodes with micro- or macro-metastases detected by sentinel lymph node biopsy.
pN1mi	Micro-metastases (approximately 200 cells, greater than 0.2 mm, but none greater than 2.0 mm).
pN1a	Metastases in one to three axillary lymph nodes, with at least one metastasis greater than 2.0 mm.
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs.
pN1c	pN1a and pN1b combined
pN2	Metastases in four to nine axillary lymph nodes, or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in four to nine axillary lymph nodes (at least one tumor deposit greater than 2.0 mm).
pN2b	Metastasis only in clinically detected internal mammary nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases in 10 or more axillary lymph nodes; or in infra-clavicular (level III axillary) lymph nodes; or in ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micro-metastases or macro-metastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supra-clavicular lymph nodes.
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infra-clavicular (level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging); or pN2a in the presence of pN1b.
pN3c	Metastases in ipsilateral supra-clavicular lymph nodes.

M0	There is no evidence of metastasis using both clinical and radiological tests.
cM0 (i+)	There is no evidence of metastasis using both clinical and radiological tests, microscopically less than 0.2 mm circulating tumor cells in blood or bone marrow and without present of tissue deposits.
M1	Evidence of metastasis confirmed by both clinical and radiological tests, with presence of either circulating tumor cells more than 0.2 mm microscopically or proven histopathology tissue invasion.

Stage	Breast cancer staging based on TNM
0	Tis, N0, M0
I	T1, N0, M0
II A	T0, N1, M0 or T1, N1, M0 or T2, N0, M0
II B	T2, N1, M0 or T3, N0, M0
IIIA	T0, N2, M0 or T1, N2, M0 or T2, N2, M0 or T3, N1, M0 or T3, N2, M0
IIIB	T4, N0, M0 or T4, N1, M0 or T4, N2, M0
IIIC	any T, N3, M0
IV	any T, any N, M1

9.2 TEMPLATES

- S1. The LBC Registry Form (i).
- S2. The follow up / visit form of LBCR (ii).
- S3. Deceased form of the LBCR (iii).
- S4. Informed Consent: S4. a. Informed consent in the English language. S4. b. Informed consent in the Arabic language

LIBYAN BREAST CANCER RIGISTRY FORM(I)

This form consists of 17 pages, please follow the manual of the LCRF and write with black pen. Consent form Must be signed before starting to fill the form. Check all pages are attached and participant ID is completed.

Section A

ICD-code C50
Participant registry LBCR-ID*:* |__|__|__|__|__|__|__|__|__|__|
Specify if this is the first primary breast cancer (first file or second file for the same participant diagnosed with breast cancer.

- ☐ *First primary breast cancer.*
- ☐ *Second primary breast cancer.*

If second primary*, please fill the in the previous patient registry ID:*
|__|__|__|__|__|__|__|__|__|__|__|__|

Section B

Person filling the form details*:*
Initial: |__|__|__| *Full name:* _____
Cell phone number: _____ *Email address:* _____
Signature: _____ *Date: DD/MM/ YYYY*

Section C

Details of participant Relative in case of required details:
*Full Name****:*** _____ *Relation:* _____
Cell phone: _____ *Address:* _____

Section D -i

Participant Details:
Full name: _____ *Address (Town, village):* _____
City/Country: _____ *Mobile (Telephone):* _____
Date of Birth: DD /MM /YYYY. *Age:* |__|__|__|
Country of birth: _____
Place of Birth: _____ *Sex:* *Male* |__| *Female* |__|

Section D -ii

Marital status please fill in only one:

- ☐ *Never been married*
- ☐ *Single*
- ☐ *Married*
- ☐ *Divorced*
- ☐ *Widow*
- ☐ *Separated*

***Participant nationality*:**

- ☐ *Libyan*
- ☐ *Not Libyan*
- ☐ *Un specified*

If not Libyan specify: _____

Specific for Libyan participant ONLY:

- ☐ *Arab*
- ☐ *Amazigh*
- ☐ *Tuareg*
- ☐ *Tebow*
- ☐ *Un specified*

Participant ID chose from below:

- ☐ *Passport number*
- ☐ *National number*
- ☐ *Driver's license*
- ☐ *Family number*
- ☐ *Others, specify: _____*

ID Number: |_|_|_|_|_|_|_|_|_|_|_|_|_|

Religion:

☐*Muslim* ☐ *Christian* ☐ *Jewish* ☐ *Hindu* ☐*Buddhist* ☐*Atheist* ☐*Unspecified*

Level of Education: (highest level of education).

- ☐ *None (Illiterate)*
- ☐ *Primary school*
- ☐ *Secondary school/ high school*
- ☐ *Collage/ University or higher*
- ☐ *Unknown*

Occupation of participant:

Please Choose from table (1) from 1-12 |__|__|

Night shifts: ☐ *Yes* ☐ *No*

If yes, years working night shifts: |__|__|

Section E -i

Participant personal habits

Does the participant use tobacco products?

- ☐ *Never had tobacco*
- ☐ *No*
- ☐ *Yes.*

If yes, please chose from below:

- ☐ *Sniffing*
- ☐ *Cigarettes*
- ☐ *Chewing*
- ☐ *Narghile (Hookah) (Shisha)*
- ☐ *Other, Specify: _____*

Number of years using tobacco: |_|_|

Amount used per day:

- ☐*Less than 3 times a day*
- ☐*3-5 times a day*
- ☐*more than 5 times a day*

If participant Stopped using tobacco

Date stopped: ***DD/MM/ YYYY***

(The amount of tobacco: one cigarette/Pinch of powder for sniffing/ one session shisha)

LBCR (i) ID|_|_|_|_|_|_|_|_|_| C50 **Doctors Initial|_|_|_|**

Section E -ii

Alcohol drinking *(units =25 ml for spirit, ~175ml of wine, ~ 500ml of beer)*

- ☐ *Never had alcohol*
- ☐ *one unit a day*
- ☐ *< 3 units a day*
- ☐ *> 3 units a day*

If participant stopped drinking:
Date stopped: ***DD/MM/ YYYY***

Section E -iii

Type of food *You can cross any type of food which is not consumed by the participant, choose from the amount of serving and amount served on daily basis from below)*

1	**2**	**3**	**4**	
☐	☐	☐	☐	*Whole grain: pasta/ bread, barley couscous, brown rice, oat, rye*
☐	☐	☐	☐	*Refined grain: pasta, bread, couscous, white rice*
☐	☐	☐	☐	*Legumes(100gm): lentil/ chickpeas/ Pease /beans*
☐	☐	☐	☐	*Carbonated drinks, sweet packed juice*
☐	☐	☐	☐	*Coffee/ Tea with sugar*
☐	☐	☐	☐	*Coffee/ Tea without sugar*
☐	☐	☐	☐	*Snacks: cakes / biscuits/ chips/ sweets / chocolates*
☐	☐	☐	☐	*Seasonal: fruits / vegetables / fresh juice (nuts or dates20-30g)*
☐	☐	☐	☐	*Honey (1-2 t / spoons)*
☐	☐	☐	☐	*Olive oil raw (2-3 t / spoons)*
☐	☐	☐	☐	*Red meat cooked: Lamb, goat, camel, beef, cured meat*
☐	☐	☐	☐	*White meat cooked (Chicken / Fish / turkey, rabbit) Eggs*
☐	☐	☐	☐	*Animal fat/ ghee/ butter, cheese, full cream milk*

(Amount of food per serving: Meat= ~100 g, Bread=~ 4 slices or1/2 baguette, pasta/rice=~ 1/2 cup).
*(**1**= 1-2 Times/Day **2**= 2-3Times/Day **3**= Once/Week **4**= Never use this type of food)*

Does participant have any food allergy: ☐ *Yes* ☐ *No* *if yes specify:* _____

Section E -iv

Choose from below regarding participant exercise habits:

- ☐ *Never exercise*
- ☐ *Minimal exercise, less than 1/2 hour a week*
- ☐ *Exercise less than 3 times a week*
- ☐ *Regular attends Gym more than 3 times a week*

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Section E -v

Choose from below regarding participant sleeping habits

- ☐ *Never takes afternoon naps*
- ☐ *Takes regular afternoon naps daily*
- ☐ *Not-interrupted night sleep*
- ☐ *Interrupted night sleep.*

If participant has interrupted night sleep: Cause: _____

If participant taking medication for sleeping: _____

Section F-i

Does the participant have a chronic medical problem (you can mark more than one)?

- ☐ *No*
- ☐ *Yes*

If yes,

- ☐ *Chronic Vascular Disease* ☐ *Diabetes Meletus* ☐ *Psychiatric Disorder* ☐ *HIV*
- ☐ *Hypertension* ☐*Asthma* ☐*Parkinson* ☐ *Liver Cirrhosis* ☐*TB*
- ☐ *Congestive Heart Failure* ☐*Chronic Obstructive Pulmonary Disease* ☐*Alzheimer*
- ☐ *Ischemic Heart Disease* ☐ *Rheumatoid Arthritis* ☐ *Dementia*
- ☐ *Hypertension* ☐*Epilepsy* ☐*Osteoporosis* ☐*Depression* ☐ *Epilepsy*
- ☐ *Myocardial Infarction* ☐ *Dyslipidemia*
- ☐ *Other medical conditions, specify:* _____

Age of participant when diagnosed: |_|_|_|

If any medication taken:

_____

Date started taking medication; DD /MM /YYYY

Does the participant have any drug allergy?

- ☐ *Yes, specify:* _____
- ☐ *No*

Comments/Changes: _____

_____

Date of changes: DD/MM/YYYY *Initials:* |_|_|_|

Section F- ii

History of surgical procedure to the breast:

- ☐ *Needle biopsy*
- ☐ *Lumpectomy*
- ☐ *Breast Implant*
- ☐ *Mastectomy*
- ☐ *Breast conserving surgery*
- ☐ *Breast Mastopexy (Breast Lift)*
- ☐ *Major duct excision*
- ☐ *Incision and drainage*
- ☐ *Breast Reconstruction*
- ☐ *Breast Reduction*
- ☐ *Augmentation*
- ☐ *Micro-dochectomy*
- ☐ *Others, specify:……..*

Date (s) conducted: DD/MM/YYYY ***Previous*** *histopathology reports: _____*

Any history of chest trauma or radiation: ☐ *Yes: _____* ☐*No*

If participant diagnosed with another primary breast cancer, please make sure noted in the first page of the LBCR (i) form.

Section F- iii

History of surgical procedure other than breast*:*

Operation: _____ Date: DD/MM/YYYY
Operation: _____ Date: DD/MM/YYYY
Operation: _____ Date: DD/MM/YYYY
Operation: _____ Date: DD/MM/YYYY
Histopathology report results: _____
Hospital name / department: _____
Comments _____

Section F- IV

History of diagnosis with Cancer (Not Breast)

Site: _____Date of diagnosis: DD/MM/YYYYY
Type: _____
Pathological stage: T N M

Did the participant receive any of the following?
Surgery: _____ Chemotherapy: _____
Radiotherapy: _____Others, specify: _____
Is the participant still on treatment?
No Yes
If Yes, specify type of treatment: _____
Started date: DD/MM/YYYY
Hospital /Centre Name: _____Unit / Department: _____
Records / File: _____Doctor in charge: _____

Section G -i

Family history of breast cancer

- ☐ *First degree*
- ☐ *Second degree*
- ☐ *Both*

Family members specify: _____

Age at diagnosis |__|__|__|

Family history of cancer (Not Breast)

- ☐ *First degree*
- ☐ *Second degree*

Family members specify: _____

Age at diagnosis |__|__|__|

Genetic counseling done:

☐ *Yes* ☐ *No*

If yes:

☐ *BRACA 1*

☐ *BRACA 2*

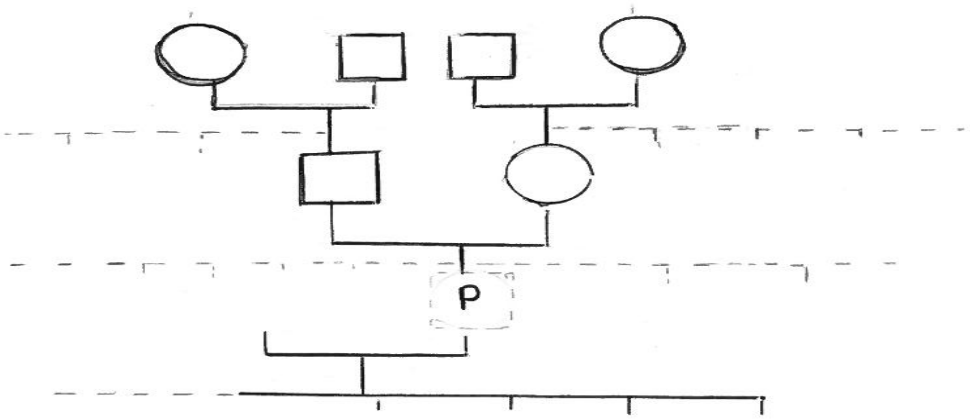
☐ *Others:* _____

Date performed: DD/MM/YYYY

Comments: _____

Section G -ii

• ***Family pedigree*** ***(Please fill in the picture using the available codes):***



Female no breast cancer	○	Male no breast cancer	□
Female with breast cancer	●	Male with breast cancer	■
Pregnant female	⊙	Dead male no BC	⊠
Mating	⌐¬	Dead male with BC	■/
Divorce	//	Dead female with BC	●/
Twins	○○	Dead female no BC	⊘

Section H -i

This section only for female participants if the participant is a male please go to Section I.

Menarche age: |_|_| *Age of first pregnancy (Full term pregnancy):* |_|_|

Number of children: |_|_| G|___ P|___| *(G= number of pregnancies, P= number of full-term deliveries)*

Did the participant breastfeed?

☐ *Yes* ☐ *No*

If Yes, (answer for the longest duration the participant was breastfeeding).

☐ *Less than one year*
☐ *Less than two years*
☐ *Less than three years*
☐ *More than 3 years*

Is the participant pregnant at the time of filling the form?

☐ *Yes* ☐ *No*

If Yes, please answer the following:

☐ *first trimester (13 weeks)*
☐ *second trimester (> 13- 21 weeks)*
☐ *third trimester (>21- >36 weeks)*

Expected date of delivery: DD/MM/ YYYY

If the participant currently breastfeeding with breast cancer:

☐ *Yes* ☐ *No*

If yes: Date started breastfeeding DD/MM/ YYYY

Any complications while breastfeeding:

☐ *Primary Breast cancer site*
☐ *Contralateral site*
☐ *Both breasts*

Type of breast complaints while breastfeeding at time of diagnosis with breast cancer (you can choose more than one answer).

☐ *Breast pain* ☐ *Nipple fissure* ☐ *Abscess* ☐ *Lump* ☐ *Change breast color*
☐ *Others, specify:* _____

LBCR (i) ID|_|_|_|_|_|_|_|_|_| C50 **Doctors Initial|_|_|**

Section H – ii

This section only for female participants if the participant is a male please go to Section I.

Is participant Menopause at time filing the form:

□ *Yes* □ *No*

If Yes, Age of participant at Menopause: |_|_|

Did participant use Hormonal Replacement Therapy (HRT):

□ *Yes, currently on treatment.*

□ *Yes, Stopped*

□ *Never*

If Yes, and still using how long the participant used HRT (circle the duration): |_|_| *Years / Months*

If the participant stopped using: Date stopped: DD/MM/ YYYY

Did participant use any type of contraceptives:

□ *Yes* □ *Never* □ *On contraceptives.*

If Yes, or in treatment answer the following:

□ *Oral tablets* □ *Injections* □*Intrauterine hormonal device* □ *Others, specify:* _____

Name of contraceptive: _____ *How long been used:* |_|_| */ Years Months*

When did participant start: DD/MM/YYYY *When did participant stopped:* DD/MM/YYYY

Comments/Changes: _____

_____

Date of changes: DD/MM/YYYY *Initials:* |_|_|_|

Section I

Does the participant have a regular breast self-examination (BSE)?

☐ *Yes* ☐ *No*

Does the participant have a regular clinical breast examination by a Doctor (CBE)?

☐ *Yes* ☐*No*

Last ultrasound report if done at any age for screening of Breast cancer:

0 I II III IV V VI *Date of Ultra-sound:* *DD/MM/YYYY*

Did the participant ever have a mammogram at the age of 40 years or above?

☐ *Never*
☐ *Yes, not regular mammograms examination*
☐ *Yes, regular mammogram examination*

If Yes, please fill in the last mammogram date and result by circling BIRADS from Table I:

0 I II III IV V VI *Date:* *DD/MM/YYYY*

Section J

History of current breast cancer.

☐ *Left Breast* ☐*Right Breast* ☐*Both Breasts*

Methods of detecting current breast cancer:

☐ *Unknown* ☐*BSE* ☐ *CBE* ☐*Mammogram (Screening)*

How long since the symptoms started, and diagnosis was made fill-in the approximate number*:*

☐ *Days:* |_|_|_| ☐*Months:* |_|_| ☐*Years:* |_|_|

Symptoms related to breast at diagnosis: You can mark more than one answer

☐ *No symptoms* ☐*Lump* ☐*Dimpling of the skin* ☐*Pain in the breast* ☐ *Ulcer in breast*
☐ *Breast changes in size* ☐*Nipple discharge (not blood)* ☐ *Nipple bleeding*
☐ *Changes of breast color* ☐*Nipple ulcer/ scaling* *Others, specify:* _____

Diagnosis was performed by:

☐ *FNAB* ☐*Core needle* ☐*Incision biopsy* ☐*Excision biopsy*
☐ *Others*_____

Cytology report of participant at diagnosis of Breast Cancer (Chose from table III and circle below result): *C1 C2 C3 C4 C5*

Histopathology report of participant at diagnosis of Breast cancer: _____

Receptor status at time of diagnosis (please write if the receptor positive/ negative):

ER: *PR:* *HER2:* *Ki67:*

LBCR (i) ID|_|_|_|_|_|_|_|_|_| C50 **Doctors Initial |_|_|_|**

Section K

Vital signs of participant at visit:

Blood pressure:|__|__|__|/|__|__|__| ***mmhg***

Pulse rate:|__|__|__| ***Beats/ minute***

Respiratory rate: |__|__|__| ***Breath/minute***

Weight: |__|__|__|. |__| ***Kg***

Hight: |__|__|__|. |__| ***cm***

BMI = ***body weight in kg***
(body height in meters) x (body weight in meters) = |__|__|

Please chose one result from BMI below:

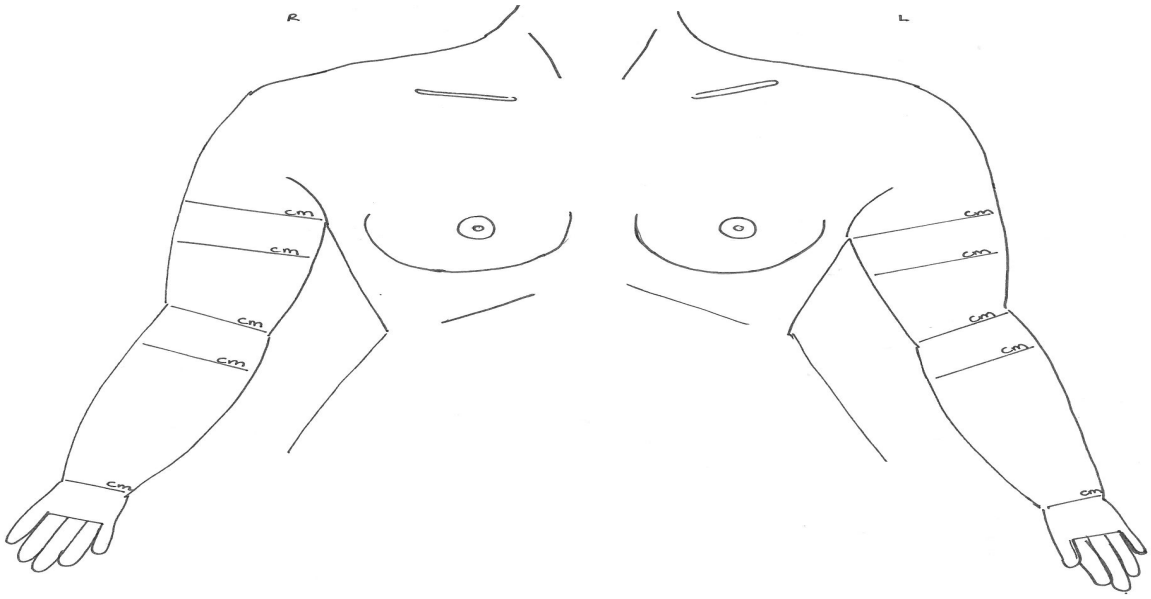
☐ *Underweight < 18.5* ☐*Normal 18.5 - 24.9* ☐*Overweight 25 - 29.9* ☐*Obese > 30*

Status of participant at time of diagnosis:

☐ *Looks healthy* ☐*Looks ill, Walking* ☐ *Looks ill, in a wheelchair*
☐ *Bed ridden, Unable to move* ☐ *Others, specify:* _____

Section L

Fill in the picture of current breast cancer and measurements of both upper limbs:



LBCR (i) ID|_|_|_|_|_|_|_|_|_| C50 **Doctors Initial|_|_|_|**

Section M

Breast Cancer Multidisciplinary Team Decision:

_____

_____

Date *DD/MM/YYYY*

Section N -i

Surgical procedures:

☐ *Yes* ☐ *No* ☐*Patient refused* ☐ *Participant not fit for surgery*

Reason not fit: _____

If participant not fit for sergery/ refused do not continue and move to section O.

Breast Primary tumor site

☐ *Left* ☐*Right* ☐*Both* ☐*Others, specify:* _____

Types of tissue removed:

Type of operation primary site(A)

☐ *Lumpectomy* ☐ *BCS/ Partial mastectomy* ☐*Simple mastectomy*

☐ *Mastectomy+ Axillary clearance* ☐*Axillary clearance only* ☐*Axillary sampling*

☐ *SLN* ☐ *Breast Reconstruction* ☐ *Others, specify:*

Lab specimens' number: |_|_|_|_|_|_|_|_|_| _____ *Date of operation:* *DD/MM/YYYY*

Type of operation primary site(B)

☐ *Lumpectomy* ☐ *BCS/ Partial mastectomy* ☐*Simple mastectomy*

☐ *Mastectomy + Axillary clearance* ☐*Axillary clearance only* ☐*Axillary sampling*

☐ *SLN* ☐ *Breast Reconstruction* ☐ *Others, specify:* _____

Lab specimens' number: |_|_|_|_|_|_|_|_|_|_____ *Date of operation:* *DD/MM/YYYY*

Type of operation primary site(C)

☐ *Lumpectomy* ☐ *BCS/ Partial mastectomy* ☐*Simple mastectomy*

☐ *Mastectomy +Axillary clearance* ☐*Axillary clearance only* ☐*Axillary sampling*

☐ *SLN* ☐ *Breast Reconstruction* ☐ *Others, specify:* _____

Lab specimens' number: |_|_|_|_|_|_|_|_|_|_____ *Date of operation:* *DD/MM/YYYY*

Type of operation primary site(D)

☐ *Lumpectomy* ☐ *BCS/ Partial mastectomy* ☐*Simple mastectomy*

☐ *Mastectomy + Axillary clearance* ☐*Axillary clearance only* ☐*Axillary sampling*

☐ *SLN* ☐ *Breast Reconstruction* ☐ *Others, specify:* _____

Lab specimens' number: |_|_|_|_|_|_|_|_|_|_____ *Date of operation:* *DD/MM/YYYY*

Section N - ii

Breast Primary Tumor Type:
☐ *Invasive* ☐*Noninvasive*

Type of Noninvasive Primary of the Breast:
☐*DCIS* ☐ *LCIS*

Type of Invasive Primary Tumor of Breast Cancer:
☐ *Ductal* ☐*Lobular* ☐*Medullary* ☐*Mucinous* ☐*Tubular* ☐ *Mixed* ☐*Inflammatory*

☐ *Papillary* ☐ *Paget's* ☐ *Malignant Phyllode* ☐ *Others, specify:* _____

Measurement of primary tumor (A) *Size of invasive tumor: _ mm X __ mm X _ mm* *Size of In-situ: __ mm X __ mm X __ mm* *Size of total lesion: __mm X __ mm X _ mm*	***Measurement of primary tumor (B)*** *Size of invasive tumor: _ mm X __ mm X _ mm* *Size of In-situ: __ mm X __ mm X __ mm* *Size of total lesion: __mm X __ mm X _ mm*
Measurement of primary tumor (C) *Size of invasive tumor: _ mm X __ mm X _ mm* *Size of In-situ: __ mm X __ mm X __ mm* *Size of total lesion: __mm X __ mm X _ mm*	***Measurement of primary tumor (D)*** *Size of invasive tumor: _ mm X __ mm X _ mm* *Size of In-situ: __ mm X __ mm X __ mm* *Size of total lesion: __mm X __ mm X _ mm*

Grade:
☐ *Well differentiated* ☐ *Intermediate differentiated* ☐*Poorly differentiated*

Lymph node Biopsy/ Clearance:
☐ *Axilla of primary breast cancer site* ☐ *Axilla of ipsilateral primary breast cancer site*
☐ *Supra clavicular primary breast cancer site* ☐*Internal mammary primary breast cancer site*
☐ *Supra clavicular of opposite site primary breast cancer* ☐*Others, specify:* _____

Method detected Lymph Nodes/ Sentinel Lymph Nodes
☐ *Palpation/ Surgical removal axillary fat only* ☐ *Blue dye /Biopsy only*
☐ *Isotope/ Biopsy only* ☐ *Both blue dye and isotopes /Biopsy*
☐ *Axillary fat removal with both blue dye and Isotope* ☐ *Unknown*

Number of nodes detected/Removed: |_|_|_|
Number of lymph node involved with cancer: |_|_|_|
Lymph Nodes with Extra capsular invasion: |_|_|_|
Date: *DD/MM/YYYY*
Receptor status:
☐ *ER:* _____ ☐ *PR:* _____ ☐ *HER2 /neu:* _____

TNM Stage (pathological stage): *T N M* |__|__|__|

Comments: _____ *Date:DD/MM/YYYY Initials:*|_|_|_|

Section O

Laboratory examination: Please fill in the latest results only.

Tumor markers: *CEA _____ ng/ml. Date: DD/MM/YYYY* *Ca 15-3 _____U/ml. Date: DD/MM/YYYY* *Ca 27.29 _____U/ml. Date: DD/MM/YYYY* *Ca 125 _____U/ml Date: DD/MM/YYYY* *Others specify: Date: DD/MM/YYYY*	***Full blood count (FBC)*** *Hemoglobin_____ Date: DD/MM/YYYY* *WBC_____ Date:DD/MM/YYYY* *RBC_____ Date: DD/MM/YYYY* *Platelets_____ Date: DD/MM/YYYY* *Other specify: _____ Date: DD/MM/YYYY*
Liver function test (LFT): *Serum bilirubin* *ALT (SGPT) _____Date: DD/MM/YYYY* *AST (SGOT) _____Date: DD/MM/YYYY* *Albumin_____ Date: DD/MM/YYYY* *PT/INR_____ Date: DD/MM/YYYY* *TP_____ Date: DD/MM/YYYY* *LDH_____ Date: DD/MM/YYYY* *Other specify: _____ Date: DD/MM/YYYY*	***Renal function test (RFT):*** *GFR _____ Date: DD/MM/YYYY* *Creatinine_____ Date: DD/MM/YYYY* *Blood urea _____ Date: DD/MM/YYYY* *Other specify: _____ Date: DD/MM/YYYY*
Serology: *HIV_____ Date: DD/MM/YYYY*	*Other tests specify/result:* *Date: DD /MM /YYYY*

Comments: _____ *Date:DD/MM/YYYY Initials:|_|_|_|*

Section P

Metastatic Workup (fill only the last results):
Latest Mammograms:
☐ *Left* ☐*Right*
Please circle the appropriate ***BIRADS*** *for each breast chose details from table 2.*

L 0 I II III IV V VI Date: *DD/MM/YYYY*

R 0 I II III IV V VI Date: *DD/MM/YYYY*

Ultrasound examination: Breast/ Axilla
*Left*_____
*Right*_____

Date: DD /MM /YYYY

Ultrasound examination: Abdomen/ Pelvis:
Results: _____
_____

Date: *DD /MM /YYYY*

X-rays examination (1):
Site: _____
Result: _____
Date: DD /MM /YYYY

X-rays examination (2):
Site: _____
Result: _____
Date: DD /MM /YYYY

Computed tomography CT scan (1):

Site: _____
Result: _____
Date: DD/ MM/ YYYY

Computed tomography CT scan (2):

Site: _____
Result: _____
Date: DD/ MM/ YYYY

MRI (Magnetic Resonant Imaging)

Site: _____

Result: _____

Date: DD/ MM /YYYY

Others investigation:

Site: _____

Result: _____

Date: DD/ MM /YYYY

PET scan (Position Emission Tomography)
Result: _____

Date: DD/MM/YYYY

Comments:_____
_____
_____

Bone Scan (Scintigraphy)
Result: _____
Date: DD /MM /YYYY

Date:DD/MM/YYYY Initials:|_|_|_|

LBCR (i) ID|_|_|_|_|_|_|_|_|_| C50 **Doctors Initial|_|_|_|**

Section Q

Chemotherapy received:

☐ *Yes* ☐ *No* ☐*Patient refused* ☐ *Participant not fit for Chemotherapy*

Reason not fit: _____

If participant not fit for chemotherapy / refused, do not continue and move to section R

Type of chemotherapy given (regime)

- ☐ *Before surgery partial cycle*
- ☐ *Before surgery full cycle*
- ☐ *Post-surgery partial cycle*
- ☐ *post-surgery full cycle*
- ☐ *Palliative*

Number of cycles before surgery: ⌊_|_| ***Number of cycles after surgery:*** ⌊⌊|

Name of drugs	***Route***	***Dose***	***Start Date***	***Stopped Date***
☐ _____			*DD/MM/YYYY*	*DD/MM/YYYY*
☐ _____			*DD/MM/YYYY*	*DD/MM/YYYY*
☐ _____			*DD/MM/YYYY*	*DD/MM/YYY*
☐ _____			*DD/MM/YYYY*	*DD/MM/YYYY*
☐ _____			*DD/MM/YYYY*	*DD/MM/YYYY*
☐ _____			*DD/MM/YYYY*	*DD/MM/YYYY*
☐ _____			*DD/MM/YYYY*	*DD/MM/YYYY*
☐ _____			*DD/MM/YYYY*	*DD/MM/YYYY*
☐ _____			*DD/MM/YYYY*	*DD/MM/YYYY*
☐ _____			*DD/MM/YYYY*	*DD/MM/YYYY*

Date started Chemotherapy DD/MM/YYYY *Date Ended Chemotherapy Treatment DD/MM/YYYY*

Comments: _____

Date:DD/MM/YYYY Initials:|_|_|_|

Section R

Radiotherapy received:

☐ *Yes* ☐ *No* ☐*Patient refused* ☐ *Participant not fit for Radiation therapy*

Reason not fit: _____

Type of management:

☐ *Palliation* ☐*Therapy (Cancer eradication)*

Dose: _____

Site

☐ *Breast of primary cancer before surgery* ☐*Supra clavicular*
☐ *Breast of primary cancer post-surgery* ☐ *Chest wall*
☐ *Axillary same site of primary breast cancer* ☐*Others, specify:* _____ _____

Date received Radiotherapy: DD/MM/YYYY
Date stopped Radiotherapy: DD/MM/YYYY

Section S

Hormonal therapy/ Target therapy received:

Hormonal Therapy

☐ *Yes* ☐ *No* ☐*Participant refused* ☐*Participant not fit.*

Reason not fit: _____

Hormonal treatment type:

☐ *Ovarian ablation by radiotherapy* ☐*Medication.*
☐ *Oophorectomy (surgical removal of ovaries)* ☐*Others, specify:* _____

If participant used any medication: ☐ *Before surgery* ☐*After surgery*

Name of drugs	*Route*	*Dose*	*Start Date*	*Stopped Date*
☐ _____			DD/MM/YYYY	DD/MM/YYYY
☐ _____			DD/MM/YYYY	DD/MM/YYYY
☐ _____			DD/MM/YYYY	DD/MM/YY

Target Therapy

☐ *Yes* ☐ *No* ☐*Participant refused* ☐*Participant not fit.*

Reason not fit: _____

If yes*, therapy started:* ☐ *Before surgery* ☐*After surgery*

Name of drugs	*Route*	*Dose*	*Start Date*	*Stopped Date*
☐ _____			DD/MM/YYYY	DD/MM/YYYY
☐ _____			DD/MM/YYYY	DD/MM/YYYY

Section T

Any other medication prescribed:

Name of drugs *Route Dose* *Start Date* *Stopped Date*

☐ _____ DD/MM/YYYY DD/MM/YYYY
☐ _____ DD/MM/YYYY DD/MM/YYYY

Any other used not prescribed treatment by the participant:

☐ _____ DD/MM/YYYY DD/MM/YYYY
☐ _____ DD/MM/YYYY DD/MM/YYYY

Is the participant registered in a trail: ☐ *Yes* ☐*No*
Trial Name: _____ *Date:DD/MM/YYYY*

Comments: _____

Section U

Any change of information please use this space and fill-in the initials and date.

_____

_____

_____

Date:DD/MM/YYYY *Initials:*|_|_|_|

LIBYAN BREAST CANCER RIGISTRY FORM (II)

This form consists of SEVEN pages, please follow the manual of the LCRF and write with black pen. Check all pages are attached and participant ID is completed.

Section A

Visit number: |__|__|__|__|__| *Date of visit: DD/MM/YYYY*

Participant LBCR- ID: |__|__|__|__|__|__|__|__|__|__|__|__|__| ***C50***

Person filling the form details/ initials:
Full name: _____ *Initials:* |__|__|__|
Place of work: _____ *Telephone number:* _____

If participant changed any contact details, please fill in below:
Address: _____ *Telephone number:* _____

Section B

Participant details for attending visit:

- ☐ *Participant attended visit as scheduled date*
- ☐ *Participant attended unscheduled visit*
- ☐ *Participant attended after contact was performed by hospital staff*
- ☐ *Participant did not attend after contact was performed by hospital*

Indication for visit:

☐ *Visit to receive treatment* ☐ *New complaint* ☐ *Routine check up*

Reason of unscheduled visit/ New complaint: _____

If Participant attended visit move to section C. If not continue answering Section B.

- ☐ *An attempt was made to contact the participant by registry team.*
- ☐ *An attempt was made to contact family member by registry team.*
- ☐ *Participant replied.*
- ☐ *Family member replied*

Reason of not attending: _____

If participant did not attend after all attempts do not continue.

LBCR (ii) ID|_|_|_|_|_|_|_|_|_| C50 **Doctors Initial|_|_|_|**

Section C

Does the participant have a new primary breast cancer*?*

☐ *Yes* ☐ *No*

If yes answer ***Section D*** *for both sexes.*
If no and the participant is a female with no new primary breast cancer answer ***Section E.***
If the participant is a male with no new primary breast cancer go to ***Section F.***

Section D

Only fill this section if the participant has a new primary breast cancer:

New primary breast cancer site:

☐ *Contralateral (Opposite side)*
☐ *Ipsilateral (same side)*

Histopathology report: _____
Date of result: *DD/MM/YYYY*
Please fill a new form for the new primary breast cancer and complete the following:
Participant New primary breast cancer LBCR-ID :|___|__|__|__|__|__|__|__|__|__|__|__|

Section E

For female participant ONLY at visit*:*

☐ *No pregnancy*
☐ *Menopause*
☐ *Pregnant after diagnosis and treatment*
☐ *Pregnant and receiving treatment*
☐ *Miscarriage/ Abortion while on treatment*
☐ *Miscarriage/ Abortion after treatment*
☐ *Delivered after treatment*
☐ *Delivered while on treatment*
☐ *Others specify:* _____

Age started menopause if participant was not menopause at start of treatment: |__|__| *years.*

Expected date of delivery if participant pregnant at time of visit: DD/MM/YYYY

Section F

Change in personal habits after diagnosis/ management/ last visit:

***Regular eating**:*

☐ *Yes* ☐*No, reason:* _____

***Regular night sleep**:*

☐ *Yes* ☐*No, why?* _____

***Returning to normal activity (work, socializing)**:*

☐ *Yes* ☐ *No, why?* _____

Change in sexual activity:

☐ *Yes, specify:* _____ ☐ *No*

Using of alternative medicine (herbs, spiritual)

☐ *yes, specify:* _____ ☐ *No*

***Others Comment**:* _____

Section G

General status:

☐ *participant apparently well* ☐ *participant sick/weak/walking*

☐ *participant on wheelchair/unable to walk without help* ☐ *Participant bed ridden*

Vital signs of participant at visit:

Blood pressure:|__|__|__|/|__|__|__| ***mmhg***

Pulse rate:|__|__|__| ***Beats/ minute***

Respiratory rate: |__|__|__| ***Breath/minute***

Weight: |__|__|__|__|__| ***Kg***

Clinical examination:

☐ *No evidence of disease* ☐*local recurrence*

☐ *New primary breast cancer* ☐ *Metastasis without local recurrence*

☐ *Metastasis with local recurrence* ☐ *Lymphedema*

☐ *Others specify:* _____

If participant has metastasis the diagnosed method was:

☐ *Clinical* ☐ *Imaging* ☐ *Cytology* ☐*Histopathology.*

Results/ Site: _____ ***Date:*** *DD/MM/YYYY*

LBCR (ii) ID|_|_|_|_|_|_|_|_|_| **C50** **Doctors Initial**|_|_|

Section H

If participant has Lymphedema

☐ *Movement of arm not disrupted* ☐ *No movement (difficult / pain).*

Methods of diagnosis:

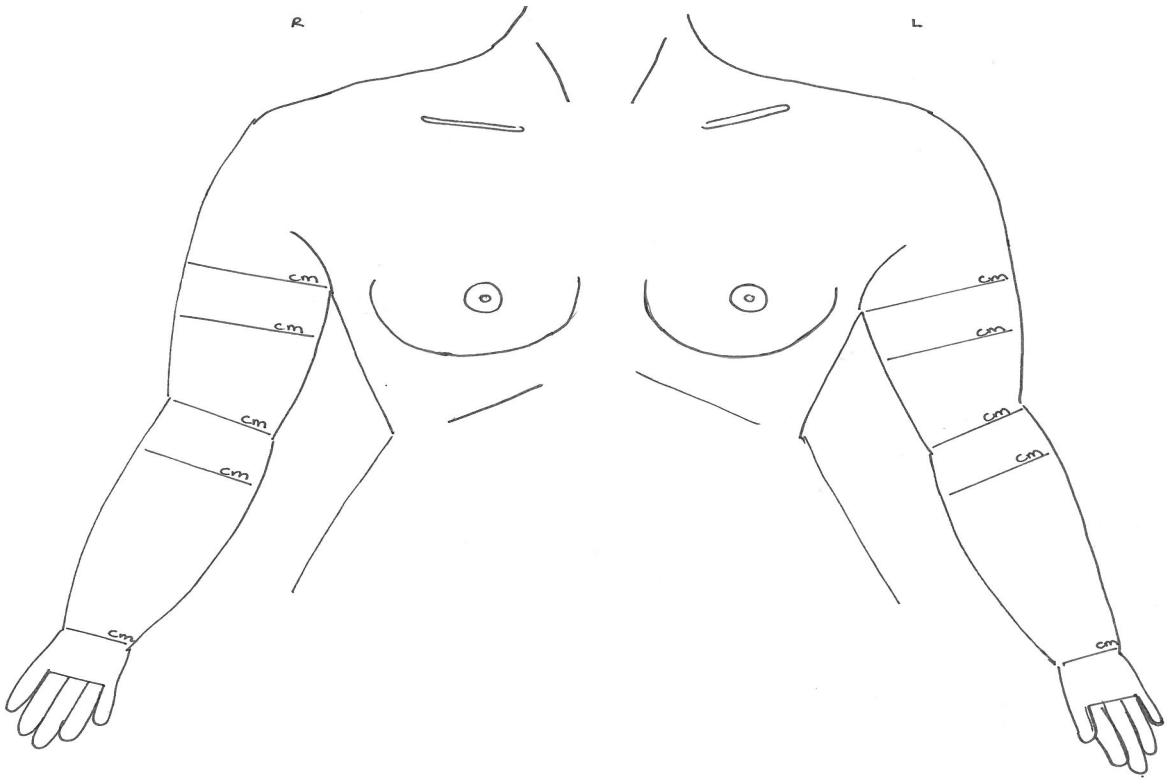
☐ *Clinical* ☐*Measurements* ☐ *Scans*

Methods used in management lymphedema:

☐ *Bandage/ Compressor garment* ☐ *Exercise/Massage therapy* ☐*Manual lymph drainage*

☐ *Surgery/Laser* ☐ *Others:* _____

Please fill in the last measurement of both sides of upper limbs/ any new finding in anterior chest wall



LBCR (ii) ID|_|_|_|_|_|_|_|_|_| C50 **Doctors Initial|_|_|_|**

Section I

Laboratory examination: Please fill in the latest results only.

Tumor markers: *CEA _____ ng/ml. Date: DD/MM/YYYY* *Ca 15-3 _____U/ml. Date: DD/MM/YYYY* *Ca 27.29 _____U/ml. Date: DD/MM/YYYY* *Ca 125 _____U/ml Date: DD/MM/YYYY* *Others specify: Date: DD/MM/YYYY*	***Full blood count (FBC)*** *Hemoglobin_____ Date: DD/MM/YYYY* *WBC_____ Date:DD/MM/YYYY* *RBC_____ Date: DD/MM/YYYY* *Platelets_____ Date: DD/MM/YYYY* *Other specify: _____ Date: DD/MM/YYYY*
Liver function test (LFT): *Serum bilirubin* *ALT (SGPT) _____Date: DD/MM/YYYY* *AST (SGOT) _____Date: DD/MM/YYYY* *Albumin_____ Date: DD/MM/YYYY* *PT/INR_____ Date: DD/MM/YYYY* *TP_____ Date: DD/MM/YYYY* *LDH_____ Date: DD/MM/YYYY* *Other specify: _____ Date: DD/MM/YYYY*	***Renal function test (RFT):*** *GFR _____ Date: DD/MM/YYYY* *Creatinine_____ Date: DD/MM/YYYY* *Blood urea _____ Date: DD/MM/YYYY* *Other specify: _____ Date: DD/MM/YYYY*
Serology: *HIV_____ Date: DD/MM/YYYY*	*Other tests specify/result:* *Date: DD /MM /YYYY*

Comments: _____ Date:DD/MM/YYYY Initials:|_|_|_|

LBCR (ii) ID|_|_|_|_|_|_|_|_|_|_| C50 **Doctors Initial|_|_|_|**

Section J

Visit Workup (fill only the last results):
Latest Mammograms:
☐ *Left* ☐*Right*
Please circle the appropriate ***BIRADS*** *for each breast chose details from table 2.*

L 0 I II III IV V VI Date: *DD/MM/YYYY*

R 0 I II III IV V VI Date: *DD/MM/YYYY*

Ultrasound examination: Breast/ Axilla
*Left*_____
*Right*_____

Date: DD /MM /YYYY

Ultrasound examination: Abdomen/ Pelvis:
Results: _____
_____

Date: DD /MM /YYYY

X-rays examination (1):
Site: _____
Result: _____
Date: DD /MM /YYYY

X-rays examination (2):
Site: _____
Result: _____
Date: DD /MM /YYYY

Computed tomography CT scan (1):

Site: _____
Result: _____
Date: DD/ MM/ YYYY

Computed tomography CT scan (2):

Site: _____
Result: _____
Date: DD/ MM/ YYYY

MRI (Magnetic Resonant Imaging)

Site: _____

Result: _____

Date: DD/ MM /YYYY

Others investigation:

Site: _____

Result: _____

Date: DD/ MM /YYYY

PET scan (Position Emission Tomography)
Result: _____

Date: DD/MM/YYYY

Comments:_____
_____
_____

Bone Scan (Scintigraphy)
Result: _____
Date: DD /MM /YYYY

Date:DD/MM/YYYY Initials:|_|_|_|

LBCR (ii) ID|_|_|_|_|_|_|_|_|_| C50 **Doctors Initial|_|_|_|**

Section K

Any complication after taking therapy:

_____

_____

Date: *DD/MM/YYYY*

Section L

Advice of visit:

Follow up: ☐ *Yes* ☐ *No*

If yes, date of next visit: *DD/MM/YYYY*

New or Change of Treatment:

☐ *Yes* ☐ *No*

If yes, specify: _____ *Drug/Dose:* _____

Date started: *DD/MM/YYYY* *Date ends:* *DD/MM/YYYY*

Reason for treatment: _____

Surgery plans:

Type: _____ *Indication:* _____

Date: *DD/MM/YYYY*

Comments:

_____

Section M

Comments/ Changes made: _____

_____

Date of changes: *DD/MM/YYYY* *Initials:*|_|_|_|

LIBYAN BREAST CANCER RIGISTRY FORM(III)

This form consists of TWO pages, please follow the manual of the LCRF and write with black pen. Check all pages are attached and participant ID is completed.

Section A

Person filling the form details/ initials:
*Full name*_____ *Initials* |__|__|__|

Place of work: _____
Date of filling the form: DD/MM/YYY

Participant registry of first primary breast cancer:
LBCR-ID |__|__|__|__|__|__|__|__|__|__|__|__|

Participant registry of second primary breast cancer:
LBCR-ID |__|__|__|__|__|__|__|__|__|__|__|__|

Source of information:
☐ *Hospital records* ☐ *Relative* ☐ *Others specify:* _____

If participant has changed address before death, please fillin the new address:
*New Address*_____ *City*_____
Date of changing address: DD /MM /YYYY

Section B

A copy of the death certificate must be in the file of deceased.
Date of death: DD/MM/YYYY *Age at time of death:* |__|__|__|

Status of last contact:
- ☐ *Apparently well*
- ☐ *On wheelchair*
- ☐ *Bed ridden*
- ☐ *Others, specify:* _____

Date of last contact: DD/MM/YYYY

LBCR (iii) ID|_|_|_|_|_|_|_|_|_| C50 **Doctors Initial|_|_|_|**

Section C

Disease status at time of death:

- ☐ *No evidence of disease at time of death*
- ☐ *there is local recurrence of cancer (lump/fungating mass)*
- ☐ *metastatic to opposite breast*
- ☐ *metastasis to other parts of body*
- ☐ *death while performing surgery*
- ☐ *death while receiving chemotherapy*
- ☐ *death while receiving radiotherapy*

If there was metastasis, please fill in the site: _____
If a histopathology was performed/results/site: _____
TNM time of death: T |__| ***N*** |__| ***M*** |__|

Place of death:

- ☐ *Unknown*
- ☐ *Home*
- ☐ *Hospital details:* _____

Cause of death:

- ☐ *Unknown*
- ☐ *Death due to primary cancer*
- ☐ *Death related to other cancer*
- ☐ *Death not related to cancer*

Death not related to cancer please specify: _____
Autopsy was performed ☐ *Yes* ☐*No*
If yes, please write findings: _____ *Date of autopsy: DD/MM/YYYY*

Any comments/ changes: _____
_____
_____
Date of changes: DD/MM/YYYY *Initials:* |_|_|_|

LIBYAN BREAST CANCER RIGISTRY CONSENT FORM

Please read/listen to the information before signing the form:

- **Why do I need to register?**

We are recording all breast cancer patients in the country by collecting your data from all medical records. We will be using your personal, laboratory, imaging results treatment that you have received and follow up list records. The purpose of registration is to calculate the number of patients with breast cancer, to help investigate the possible causes of the disease and distribution, occurrence in specific groups, also related risks that can aggravate the breast cancer. This registry will not affect your treatment, there will be no change in your treatment plan as advised by your specialist.

- **Are there any risks or disadvantages for me?**

There will be no risks or any disadvantages from registering; we only need your detail data regarding diagnosis and treatment.

- **Are there any benefits for me?**

There are no additional benefits for you or any other participant, and there will be no payment for all participants taking part in the registry. You will be treated no difference to anyone who does not take part this registration.

- **What if I would like to stop to participate?**

You are free to participate and decide to withdraw at any time and not to complete the follow-up forms. If you miss any fallow-up, an attempt will be made to contact, you or your relative to

remind you. Your follow- up, management, and care will not change from any other participant and will continue as advised by your specialist now and in the future.

- **Who will have access to my information?**

All data will be stored and de-identified. The investigators only have access to the coding. Any additional staff or researches will see your data without your name details.

In case of a missed visit, an attempt to call you or your documented relative for further information needed, and this information will be recorded (written) to your form.

- **You are free to ask any questions at any time.**

Dr. Muna AB Owen Abulkasim

Tel: 061 070 1366

Email address: owenmuna@yahoo.com

LIBYAN BREAST CANCER RIGISTRY CONSENT FORM

Please read/ Listen

I have read/ listen and understood the above information, and all my questions have been answered. I understand I was selected to participate and have the right to withdraw at any time. I will receive my full treatment as advised by my oncologist in case I would like to discontinue in providing any personal information. I am aware that my information will be used in medical research for education purpose in an attempt to help patients suffering from breast cancer. I agree to allow my results to be published in medical journals or books and will be available at the Universities for public use.

Participant full name: _____

Date: *DD/MM/YYYY* Signature/ Fingerprint: _____

In case of the participant cannot write or read:

Name of person: _____ Relation: _____

Date: *DD/MM/YYYY* Cell phone: _____ Signature: _____

Name of witness: _____

Date: *DD/MM/YYYY* Signature: _____

The person completing the form: _____

Place of work: _____ Cell phone: _____

Date: *DD/MM/YYYY* Email address: _____ Signature: _____

معلومات هامة قبل التسجيل

لماذا أحتاج للتسجيل؟

نحن نسجل جميع مرضي سرطان الثدي في البلد من خلال جمع بياناتك الشخصية من جميع السجلات الطبية الخاصة (نتائج المختبر نتائج التصوير والأشعة وسجلات المتابعة) الغرض من التسجيل هو معرفة عدد المرضي الذين يعانون من سرطان الثدي للمساعدة في التحقيق اسباب انتشاره وتوزيعه وحدوثه، وكذالك المخاطر ذات الصلة التي يمكن ان تؤدي الي تفاقم سرطان الثدي. لن يؤثر هذا السجل على علاجك ولن يكون هناك اي تغير في خطة العلاج كما هو موضح من قبل طبيبك المختص

هل هناك أي مخاطر بالنسبة لي؟

.لن يكون هناك أي مخاطر من التسجيل نحتاج فقط البيانات الخاصة بك فيما يتعلق بالتشخيص والعلاج

هل هناك أي فوائد لي؟

لا توجد فوائد إضافية لك أو لأي مشارك آخر ولن يكون هناك أي مدفوعات لجميع المشاركين في التسجيل لن يكون هناك فرق في التعامل مع أي شخص لا يشارك في هذا التسجيل

ماذا لو كنت أرغب في التوقف عن المشاركة؟

لديك الحق في الانسحاب في أي وقت والحق في رفض إعطاء أي معلومات لإكمال نماذج المتابعة. إذا فاتتك أي متابعة فستتم محاولة .الاتصال بك لتذكيرك. لن تتغيّر المتابعة أوالرعاية وستستمر كما هو منصوص عليه من قبل طبيبك المختص الآن وفي المستقبل

من سيكون لديه حق الوصول إلى معلوماتي؟

سيتم تخزين جميع البيانات برموز والأشخاص المسؤولين عن التسجيل الذين يعملون في وحدة التسجيل هم من لديهم فقط إمكانية الوصول إلى الترميز في حالة عدم حضورك لزيارة الطبيب سنحاول الاتصال بك أو أقرب الاقارب للحصول على مزيد من المعلومات المطلوبة، وسيتم تسجيل هذه المعلومات الي النموذج الخاص بك

يمكن الأسئلة و الاستفسار:
د. مني عبد السلام عون ابو القاسم
البريد الالكتروني:owenmuna@yahoo.com

يرجي القراءة او الاستماع

لقد قرات/استمعت وفهمت المعلومات الواردة اعلاه، وتمت الاجابة على جميع أسئلتي، وافهم انني قد تم اختياري للمشاركة ولدي الحق في الانسحاب في اي وقت، وسوف اتلقي العلاج الكامل الذي تقدم به طبيب الاورام في حال رغبت في التوقف عن تقديم اي معلومات شخصيه. أدرك ان المعلومات ستستخدم في الابحاث الطبية والعلمية لمساعدة المرضي الذين يعانون من سرطان الثدي. واوافق على السماح بنشر نتائجي في المجلات او الكتب الطبية وستكون متاحة في الجامعات للاستخدام العام

اسم المشارك بالكامل:

بصمة: التوقيع: ***تاريخ:***

في حالة عدم تمكن المشارك من الكتابة أو القراءة:

اسم الشخص: ***علاقة الشخص بالمشارك :***

رقم الهاتف ***التوقيع*** ***تاريخ:***

اسم الشاهد:

التوقيع: ***تاريخ:***

اسم الشخص الذي قام بأخذ البيانات

الهاتف الخلوي: ***مكان العمل***

عنوان بريد الكتروني:

التوقيع: ***تاريخ:***

9. LIBYAN BREAST CANCER RIGISTRY PROJECT COORDINATORS

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CHAPTER SIX

THESIS CONCLUDING REMARKS

THESIS CONCLUDING REMARKS

Breast cancer incidence and mortality differ across regions and between sexes; however, it remains the most familiar diagnosed cancer in women and one of the leading causes of cancer deaths across all continents.

Principal findings

First, the findings of this thesis have addressed the prevalence of breast cancer in Africa. We propose that it serves as a resource for providing baseline figures for future local and national comparisons.

Second, this report on the design of the Libyan Breast Cancer Registry includes ready and accessible information to serve as a template for present and future use of medical elements and researchers in the field of science.

Implications for policy and future research

Growing incidence and mortality rates of breast cancer in Africa provide clear evidence that this part of the world does not yet have an appropriate management strategy. In consideration of the above, African countries should embark on awareness and early prevention of the disease, through proper identification methods and reduced exposure to established risk factors in conjunction with appropriately-sensitive and highly specific diagnostic methods for young adults and advance suitable treatments. Coupled with a high quality registry, such as the Libyan Breast Cancer Registry, will provide meaningful evidence for the control of breast cancer in Africa and will have an unquantifiable effect on the national development of African countries.