BURDEN AND CLINICAL-PATHOLOGICAL CHARACTERISTICS OF BILATERAL BREAST CANCER AT THE KENYATTA NATIONAL HOSPITAL - A FIVE YEAR REVIEW

PRINCIPAL INVESTIGATOR:
DR. STANLEY THUITA NG'ANG'A

H58/7260/2017

A dissertation submitted in Partial Fulfillment for the award of Master of Medicine in General Surgery, University of Nairobi.

26th MARCH 2022

STUDENT'S DECLARATION

I hereby declare that this dissertation is my original work and has not been presented for a degree in any other university. Wherever I have quoted another person's work, I have accordingly acknowledged and referenced.

Dr. Stanley Thuita Ng'ang'a

Signed: …… Date: ……26/4/2022…….

ACKNOWLEDGEMENT

First of all, I want to thank God almighty for seeing me through training and development of this paper. My sincere gratitude goes to my supervisors Dr. Elly Nyaim Opot and the late Dr. Joseph Wangombe Githaiga for the guidance and insights to making this dissertation a success. I am also thankful to my family and friends for the unconditional support in this intense training.

DECLARATION OF ORIGINALITY

NAME	Dr. Stanley Thuita Ng'ang'a
REGISTRATION NUMBER	H58/7260/2017
COLLEGE	Health Sciences
FACULTY	Medicine
DEPARTMENT	General Surgery
COURSE	Masters of Medicine in General Surgery
TITLE	Burden and clinical-pathological characteristics of bilateral breast cancer at the Kenyatta National Hospital - a five year review

1. I declare that this thesis and the work presented in it are my own.
2. I confirm that this work was done mainly while in candidature for a postgraduate degree at this University.
3. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated.
4. Where I have consulted the published work of others, this is always clearly attributed.
5. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
6. I have acknowledged all main sources of help. Where the use of external databases has been availed, there the attributes were thoroughly checked the nature of such datasets are open

SIGNED **DATE**

CERTIFICATE OF SUPERVISORS

This Dissertation has been submitted with our approval as the university supervisors:

Dr. Elly Nyaim Opot

MBChB (U.O.N), M.Med General Surgery (U.O.N), FCS (ECSA)

Senior Lecturer in General Surgery, Department of Surgery

University of Nairobi.

Signed: ..... Date: 25/4/2022

Dr. Joseph Wangombe Githaiga

MBChB (U.O.N), M.MED General Surgery (U.O.N), FCS (ESCA) Deceased

Senior Lecturer in General Surgery, Department of Surgery,

University of Nairobi

Signed: ..... Date: 25/4/2022

DEPARTMENTAL APPROVAL

The research proposal was presented and submitted at the departmental meeting held on **23rd September 2021** at the University of Nairobi. It was subsequently approved by the Kenyatta National Hospital and University of Nairobi Ethics and Research Committee (KNH/UON ERC) on **06th December 2021**.This dissertation is herby submitted for examination with my approval as the Chairman, Department of Surgery.

Dr. Julius G.Kiboi

Senior Lecturer and Consultant Neurosurgeon

Chairman

Department of Surgery

University of Nairobi

Signed Date

LIST OF ABBREVIATIONS AND ACRONYMS

BiBc	BILATERAL BREAST CANCER
BRCA	BREAST CANCER GENE
EMA	EPITHELIAL MEMBRANE ANTIGEN
ER	ESTROGEN RECEPTOR
HER 2	HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2
I.H.C.	IMMUNOHISTOCHEMISTRY
K.N.H.	KENYATTA NATIONAL HOSPITAL
MFGM	MILK FAT GLOBULE MEMBRANE
MDT	MULTI DISCIPLINARY TEAM
PR	PROGESTERONE RECEPTOR
PSBBC	PRIMARY SYNCHRONOUS BILATERAL BREAST CANCER
SMA	SMOOTH MUSCLE ACTIN
T.N.M	TUMOR, NODE, METASTASIS
UON	UNIVERSITY OF NAIROBI

OPERATIONAL DEFINITION OF TERMS

Synchronous	contra lateral breast cancer diagnosed within one year of previous breast cancer
Metachronous	contra lateral breast cancer diagnosed after one year of previous breast cancer.

LIST OF TABLES AND FIGURES

TABLE OF CONTENTS

Contents

ABSTRACT

Study background: Bilateral breast cancer is an infrequent finding in our setup. As such, not many studies have been carried out on this. The information gathered from this study will be used to guide on management of such patients, prognosticate the outcome and even guide on follow up based on the frequency, prognosis, histological and immunohistopathological features, and therapeutic modalities.

Broad objective: To determine the burden and clinical-pathological characteristics of Bilateral Breast Cancer at the Kenyatta National Hospital over a five-year period.

Study design and Site: This was a descriptive retrospective study covering a period of five years which coincided with the existence of the breast MDT at K.N.H. The study was conducted at K.N.H. , this being a national referral hospital that attends to many breast cancer patients. It is a better representation of the disease burden and likely outcomes can be reached due to the diversity of patients seeking treatment at K.N.H. It also serves as the teaching hospital for the UoN, Faculty of Health Sciences, for both the undergraduate and postgraduate programs.

Materials and Method: Data from medical records of patients who had been treated for bilateral breast cancer for the past five years at K.N.H. was retrieved. The data points were on the demographic findings, family history, treatment modalities, staging, histopathology, and immunohistochemistry.

Data Management: Data was checked for completeness and accuracy prior to entry into the Microsoft Excel Spreadsheet, thereafter, transferred to the SPSS version 23 for analysis. If the p-value of a statistical test is found to be lower than 0.05, it was be considered substantial. Where applicable, the odds ratios and their corresponding 95% confidence interval were reported.

Expected main outcome measure (Utility of the study): This study's results will stimulate the process of developing guidelines on management of patients with bilateral breast cancer in our setup.

Results: The study obtained 29 files for the period of five years (2017-2021). Eight files were excluded due to missing data and relevant information. The fourth decade was the most affected period with a mean age of forty-two years. It took approximately 24 months from time of

diagnosis to development of contra lateral tumor. Metachronous tumors were the commonest at 71.4% while synchronous tumors were 28.6%. Invasive ductal carcinoma was the only carcinoma detected and the larger the primary tumor the more the chance of developing contra lateral breast malignancy (>5cm higher risk). Nodal involvement did not have a direct correlation with development of BiBc. Patients with BiBc frequently presented with distant metastasis to other organs as compared to when the tumor was unilateral and immunohistochemistry of both tumors was similar for all the patients.

Conclusion: Bilateral breast malignancy is an uncommon entity in our setup occurring mostly in the fourth decade of life with an average diagnostic period of two years from time of primary breast cancer diagnosis. Risk factors include age, patients with stage three and four tumors and invasive ductal carcinoma diagnosis on pathology. Bilateral breast malignancies carry a higher risk of metastasis to other organs and close follow up is warranted. Since immunohistochemical markers appear to be similar between primary malignancy and the contra lateral malignancy, there needs to be a revision in terms of treatment as there is a chance that both tumors share similar histopathological aspects.

1.0: INTRODUCTION

Studies show that cancer of the breast is the most prevalent cancer in women globally (1). Locally, in Kenya, breast cancer accounts for twenty-three percent of cancer mortality amongst women. It mainly affects young to middle-aged women in the thirty-five-to-fifty-five-year age groups and has a prevalence of 34/100,000. (1) The risk for developing a separate primary cancer in the contra lateral breast in a breast cancer patients' life increases two- to six-fold over the course of their life, which corresponds to a risk of 0·3–1·0% per year. (2) Moreover, contra lateral breast cancer is increasingly likely in women who have already had primary breast cancer. Bilateral Breast Cancer (BiBC) is classified as synchronous or metachronous, premised on the period between the occurrence of primary and second breast cancers. (2, 6, 7) The cut-off for synchronization is usually 3 to 6 months. Contra lateral breast cancer identified at more than a 6-month interval is known as metachronous breast cancer. (2)

The etiology of BiBC is of interest because some risk factors, such as a family history of breast cancer, are common between the initial and recurring event, while others, such as radiotherapy, may be unique to the second main. (3) Knowing the origins of contra lateral breast cancer should assist in pinpointing people who have a higher likelihood of developing the disease and providing clarity on the role of genetic, hormonal, and environmental factors in the occurrence of breast cancer. The knowledge should also aid in the tracking of the impact of early breast cancer treatments.

Primary synchronous bilateral breast cancer (PSBBC) is a rare occurrence; its prevalence is estimated to range between 0.3 to 12 percent. (22) The substantial disparity can be explained by the diverse classifications used to describe bilateral breast cancer. Some clinicians describe synchronous bilateral breast cancer as contra lateral cancer discovered within a year. Others define "synchronous bilateral breast cancers" as tumors found within three months of each other. (4, 5) Unlike unilateral breast cancer, there are no specific treatment guidelines for Bibc.

Diagnostic criteria and management strategies are among the grounds of controversy in the field of BiBc; thus, the need to address these concerns by reviewing the clinical characteristics, treatment patterns, and outcomes of bilateral breast cancer patients.

Second primary breast cancers have been found in the contra lateral breast at rates ranging from 1.4 percent to 12 percent. (6) A variety of factors have been blamed for the overall rise in bilateral breast cancer incidence. Foremost, the rate of contra lateral breast carcinoma is anticipated to increase due to overall improvement of survival in the time between the first diagnoses to the lengthier risk intermission that follows. (7) Cancer of the contra lateral breast is the most prevalent second malignancy in patients with breast carcinoma. (7) Secondly, breakthroughs in detection may account for the rise in cases, as malignancies are discovered at an earlier stage. Null parity, being younger at the incidence of the initial breast cancer, having lobular histology, and having multicentric first breast cancer are all risk factors that increase the likelihood of this predisposition. (4, 6, 7, 13) A family history plays a part in the etiology of bilateral breast cancer. (2) Females who have a first-degree relative diagnosed with breast cancer at a young age had an increased chance of acquiring bilateral breast carcinoma. (2) Furthermore, according to multiple studies, young females whose treatment for illnesses like Hodgkin disease, postpartum mastitis, T.B., and other illnesses involved irradiation had an increased risk for developing unilateral and bilateral breast carcinomas. (6)

In 1984, the metrics for diagnosing a second primary cancer were suggested by Chaudary et al. as: (5)

1. Concrete and irreproachable evidence of carcinoma present in situ in the contralateral tumor.
2. Histological difference between the breast tumors of the first and second cancers.
3. The amount of tumor histological differentiation in the recurring cancer is substantially greater than that of the first breast lesion.
4. Lack of evidence of local, regional or distant metastases from the cancer in the ipsilateral breast.

There is no conclusive data on the clinical-pathological characteristics of this disease given the differences in definition, and we do not have data in our context. This study aimed to determine the burden and clinical-pathological characteristics of Bilateral Breast Cancer at the Kenyatta National Hospital- a five-year review.

2.0: LITERATURE REVIEW

Contralateral breast cancer can be synchronous or metachronous and can be a secondary malignancy or a metastatic lesion. Pathologic parameters are used to determine if contralateral breast cancer is a metastatic lesion or an original secondary tumor. (2) In the United States, bilateral breast carcinoma accounts for only a small percentage of all breast cancer cases diagnosed each year. (2) In the scientific literature, there has been discussion about the occurrence and descriptors of bilateral breast cancer. Breast cancer in the index breast, a positive family history of breast cancer, a first cancer diagnosis at a young age, and BRCA genetic mutations are all factors that facilitate bilateral breast cancer. (2,6,7,9,13) Significant differences were found between Unilateral and Bilateral breast cancer patients in terms of age, family history of breast cancer, stage of the disease, histologic types, and tumor grade. (3) Patients under the age of 50 with a positive family history of breast cancer and who presented at a later stage of the disease are more likely to have BiBC. Besides, BiBC is substantially more common in people who have developed invasive lobular carcinoma and well-differentiated tumor grades. (4, 6-7, 13)

2.1 Demographic Characteristics

The risk of BiBC in patients with operable breast cancer ranged from 6% to 8.9%. Early identification of primary breast cancer has been linked to a higher prevalence of bilateral breast cancer, according to several experts. BiBC is prevalent in women under 50 than unilateral breast cancer, which is diagnosed at an average age of 63.5 years. (3-4)

Several studies have found that the age at the time of the initial diagnosis is the essential predictor of contralateral breast cancer. (3, 6-7) As a woman approaches the age of her first primary breast cancer, the chances of developing a second primary breast cancer grow. The incidence of BiBC dropped rapidly with increasing age at the initial main diagnosis, owing to the quick exhaustion of a vulnerable group. The actuality that patients with a family history of breast cancer acquire their disease at a younger age, or the reality that patients with a family narrative of breast cancer acquire it at a younger age, could explain why they have a reduced risk as they age. Uyisenga et al. (8) found that primary cancer strikes at a younger age in Sub-Saharan Africa, with a mean age of 49 (SD = 13) and the majority of patients (57.2%) under 50,

compared to 42.8 percent over 50. Furthermore, 47.8% of all instances of breast cancer were identified between the ages of 35 and 50; thus, explaining the rate of increased chances of contralateral breast cancer.

A family narrative of breast cancer has been associated with an elevated risk of contralateral breast cancer in various studies. (9-10) the effects of family history are most noticeable in women who had a first-degree relative who had been affected. According to Reiner et al. (2), having a sister who develops breast cancer raises the likelihood of developing contralateral breast cancer more than when it is the mother who is affected. In older women, however, this trend may be reversed. When both mother and sister are affected, the odds ratio is 5.27; however, the 95 percent confidence interval is wide (0.97–28.8) due to the limited number of participants. Females with a mother who had developed bilateral breast cancer and a younger sister or mother at the period of diagnosis had an increased chance of also developing contralateral breast cancer. (20- 21)

Furthermore, Qian et al. (11) found that race plays a vital role in predicting the risk of contralateral breast cancer. African American women had a greater incidence and risk of second breast cancer as compared to Caucasian or Asian/Pacific Islander females. Furthermore, other studies discovered a racial difference in the susceptibility of second main breast cancer, a finding that could be elucidated by an assorted blend of genetic or biologic, clinical, and socioeconomic factors. Some genetic differences in BRCA1, BRCA2, and p53 mutations have been linked to differing clinical characteristics and tumor prognosis between African Americans and Caucasians in the United States. Besides, Balekouzou et al. (12) noted that in any race, lower socioeconomic status is associated with worse tumor clinical features, improper treatments, and reduced healthcare consumption prior to and after the first primary B.C. This observation is prevalent in Africa, where most families come from lower economic statuses.

2.2 Tumor Histology

In terms of histopathological and biological properties, contralateral breast cancer has yet to be discovered. In fact, it is unknown whether it is a secondary tumor that develops after the main tumor. A contralateral tumor can result from one cell source that engenders the secondary metastatic propagation of cancer cells to the other breast or from a hormonal milieu that supports

identical biologic and pathologic features in independent tumor centers in the two breasts. It should be noted that the existence of an intraductal component, discrete histologies, a single clonal origin, and differing degrees of differentiation amongst the tumors are all indicators that they are distinct tumors. Second primary breast cancer is more prevalent in women with lobular histology than in women with ductal histology, implying that patients with invasive lobular breast cancer require more frequent diagnostic procedures and surveillance to detect contralateral breast cancer early. (11)

Several studies discovered that infiltrating ductal carcinoma was the most prevalent histology type, approximately 78 percent of all cases. (12-13) In synchronous tumors, the rate of the same histological type is higher than in metachronous tumors. Similarly, the rate of histological grade concordance in synchronous tumors is higher than in metachronous cancers. Tumors with a high intraductal component are higher in synchronous than in metachronous cancer tumors. Additionally, Kotecha et al. (14) found that in synchronous cancers, estrogen receptor expression concordance and the progesterone receptor expression concordance are higher than in metachronous malignancies. In terms of progesterone receptor status, there was a considerable difference in expression concordance rates between synchronous and metachronous cancers.

A first primary breast cancer with lobular histology is linked to an increased incidence of contralateral breast cancer. This could be due to underlying dissonances in their biological characteristics and behavior and/or origin of lobular cell versus ductal cell cancers. (14) After controlling for various characteristics, a lobular constituent of the first breast cancer was linked to an almost 2-fold greater probability of having contralateral breast cancer, a probability that was independent of whether it was invasive or in situ. Reiner et al. (2) discovered that the invasive lobular histological type was linked to a higher incidence of contralateral breast cancer, despite the limited number of in situ cases. Lobular carcinoma of the initial primary was only linked to an increased risk of contralateral breast cancer in synchronous instances, but not in asynchronous cases. The risk of getting a primary lobular carcinoma for the first time is only slightly higher than the chance of developing a primary ductal carcinoma for the first time. (15) Contralateral ductal breast cancer has become more common, probably as a result of enhanced monitoring of females who have already been diagnosed with breast cancer, especially in the first year after cancer determination.

2.3 Tumour Immunohistochemistry

Immunohistochemistry (I.H.C.) is utilized to describe and categorize intracellular proteins and numerous cell surfaces in all tissues. Distinctive markers, or typically, panels of numerous characteristic marker proteins, are employed to identify different tumor subtypes, substantiate tissue of origin, differentiate metastatic from the first and dominant tumor, and allow sufficient information about the tumor to be uncovered, which is useful for prognosis, therapy reaction prediction, or assessing any remaining tumor after treatment.

According to Ramião et al. (17), normal glandular breast tissue comprises luminal, basal, and myoepithelial cells, all of which manifest differing protein subsets. Luminal cells manifest the following antigens: C.K. 7, -8, -18, -19, milk fat globule membrane antigen (MFGM), -lactalbumin, epithelial membrane antigen (E.M.A.), progesterone receptor (P.R.), and estrogen receptor (E.R.). Myoepithelial cells, as well as basal cell type C.K.s, express smooth muscle actin (S.M.A.), p63 (C.K. 5&6, -14, -17), and calponin, S100.

Breast cancer is divided into subgroups. The Luminal A" subtype is defined by high E.R. expression but no HER2 expression. E.R. expression is lower in luminal B and C malignancies. Subtype B is defined by the expression of E.R. with or without HER2. The Luminal C subtype is characterized by the expression of a group of genes whose roles are unknown. Triple-negative and basal subtypes can further be differentiated by their genetic characteristics and HER-2 enriched subtypes by over expression of these receptors. (10,20) In Kenya, according to Githinji (21), E.R.-positive cancers are more prevalent than P.R. and HER2-positive tumors; similarly, Luminal A subtype is more common than luminal B and HER2 enriched subtypes of breast cancers. Qian et al. established that mixed histology presented a risk for developing contralateral breast cancer. Additionally, Yang et al. failed to find a substantial difference in the nodular status, T.N.M. stage, histologic type, E.R., PR, and HER-2 status between the first and second breast cancer of the BiBC. (19)

A different study showed no differences in the concurrence rate of the appearance and expression of estrogen receptors in both synchronous and metachronous bilateral breast cancers. (10) In contrast, for synchronous cancers, the concurrence rate for progesterone receptor expression was considerably higher. Moreover, investigating bilateral breast cancers through staining for *cer*bB-

2 revealed an expression rate of 44% in all tumor tissues, regardless of whether they were the initial or the second tumors. This frequency was higher than the *cer*bB-2 expression rate for unilateral breast cancer, which was found to be 26%. These findings suggested that the higher mortality rate in patients with bilateral synchronous breast cancer is firmly linked to the over-expression of *cer*bB-2, as compared to patients with unilateral breast cancer. (10)

2.4 Statement of the problem

Currently, cancer of the breast is a primary cause of mortality and morbidity of women worldwide, with each woman diagnosed with breast cancer in one breast having an eternal concern or worry of tumor in the opposite breast. Evidence suggests family history, histology, age, and immunohistochemistry as the main factors associated with BiBC occurrences. (2,-7, 13) Could this be the case in our setup?

It is with the intention of exploring these factors that this study was carried out with the hope that more information on bilateral breast cancer will stimulate the process of developing clear guidelines on the management of this condition in our setup

2.5 Justification of the study

This study forms a baseline for future studies on BiBc. It will enable the evaluation of bilateral breast cancer in terms of demographics, risk factors for BiBc, treatment protocols and management, and prevention of future occurrences as no work has been done on this, and there is a big knowledge gap.

The protocols are expected to improve the detection of and improvements in the outcomes of management of bilateral breast disease.

2.6 Research objectives

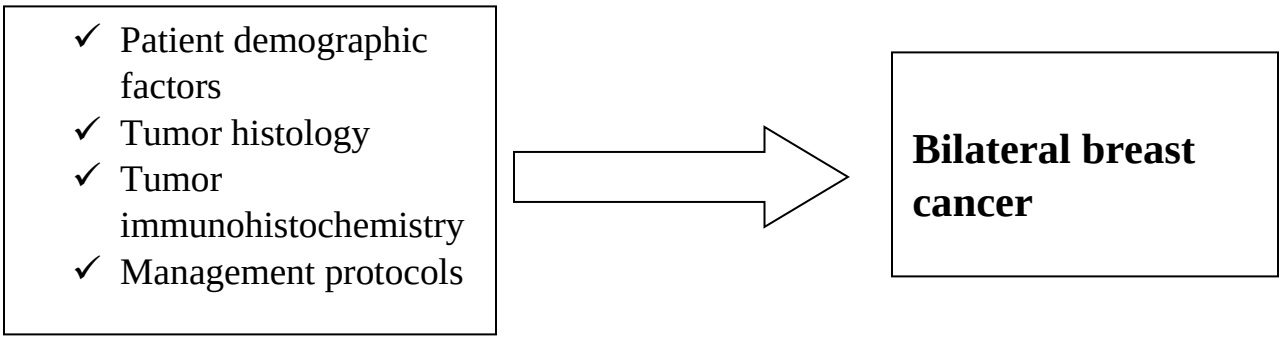
2.6.1 Broad objective

To determine the burden and clinical-pathological characteristics of Bilateral Breast Cancer at the Kenyatta National Hospital over the past five years.

2.6.2 Specific objectives

1) To determine the time prevalence of bilateral breast cancer as seen at K.N.H.
2) To determine the factors associated with the occurrence of bilateral breast cancer,
3) To determine the histopathological diagnosis and immunohistochemistry subtypes in bilateral breast cancer as seen in K.N.H.
4) To determine management strategies used for bilateral breast cancer in KNH

2.7 Conceptual Framework



3.0: METHODOLOGY

3.1: Study design

This was a descriptive retrospective study for a period of five years.

3.2: Study area

The study was conducted at K.N.H., which is the national referral hospital and attends to many breast cancer patients. A better representation of the disease burden and likely outcomes can be reached due to the diversity of patients seeking treatment at K.N.H. It is also a 2000 bed national teaching and referral hospital which serves as the teaching hospital for the UoN, Faculty of Health Sciences, for both the undergraduate and postgraduate programs.

3.3: Sample Size

This was a census study.

3.4: Study population

Data records of patients with bilateral breast cancer as seen at K.N.H. for the past five years. From the year 2017 to the year 2021.

3.4.1: Inclusion criteria

All records of patients with bilateral breast cancer diagnoses for the past five years were included.

3.4.2: Exclusion criteria

Incomplete or missing records

3.5: Sample size Determination and Formula

This was a census/population study.

3.6: Data Collection Procedure

The principal researcher, in coordination with his assistants who were graduates in the medical field, and had data collection experience through training by the researcher, collected the data from the patient records and facilitated entry into statistical programs for analysis.

3.7: Data Management and Analysis

Data from the pre-filled questionnaires (age, family history, stage, comorbidities, histology, immunohistochemistry, and treatment administered) were checked for completeness and accuracy prior to entry into the Microsoft Excel Spreadsheet, thereafter, transferred to the SPSS version 23 for analysis.

After analysis, the findings from the categorical data were represented as frequencies and proportions, while that from the continuous data was depicted through means and the corresponding standard deviations.

If the p-value of a statistical test was found to be lower than 0.05, it was considered substantial. Where applicable, the odds ratios and their corresponding 95% confidence interval were reported.

3.8: Ethical Considerations

Permission to conduct this research was sought from K.N.H. and UoN Ethics Research Committee. Data from the study was accessible only to the principal researcher, research assistant, and data analysis manager. All data was stored in a password-protected drive.

3.9: Study Results: Dissemination Plan of Study Findings

The study results will be disseminated to the UoN repository and the K.N.H./ UoN research ethics committee, and to the Department of surgery. The dissertation will be submitted for publication to relevant journals.

.

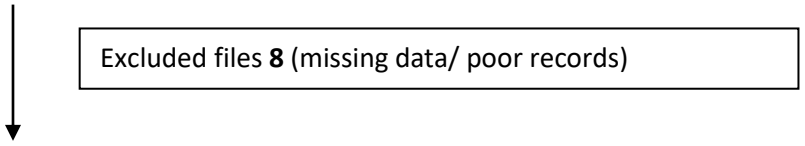
3.9.1: Study Limitations

Factors that affected this study included; incomplete or missing records and different management of patients with breast cancer amongst surgeons, oncologists and radio-oncologists.

4.0 RESULTS

Out of 1000 files that were reviewed for the past five years (2017-2021), 21 cases of bilateral breast cancer were identified. Giving a period prevalence of 2.1%.

Eligible files of all patients with bilateral breast cancer from the study period **29** files



Data entry and analysis **21** files

Figure 1: Flowchart on file retrieval

All the cases studied were female patients. No male patients were diagnosed with bilateral breast cancer.

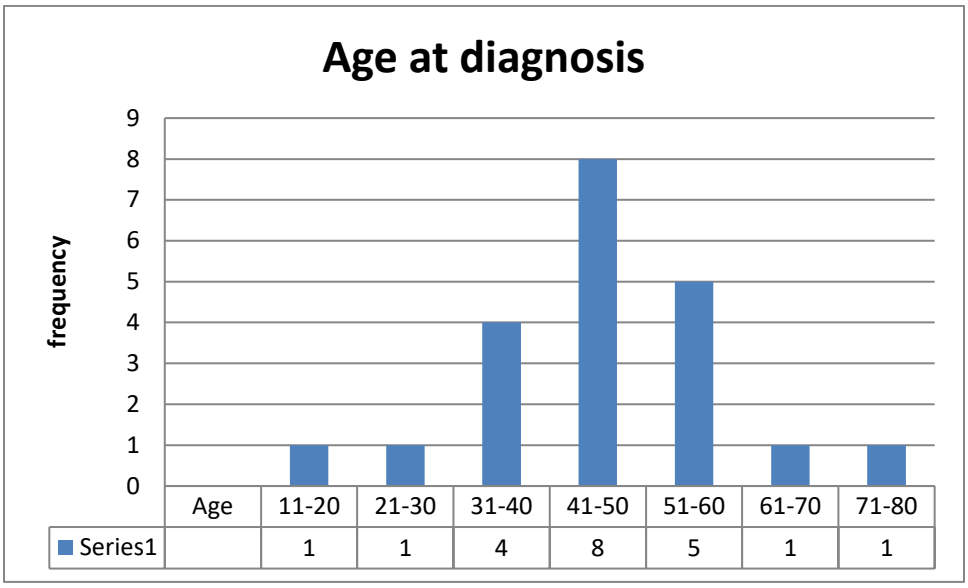


Figure 2: Age at contra lateral breast cancer diagnosis

Majority of the patients were between the ages of forty to fifty years at the time of diagnosis

The mean age at primary diagnosis was 42 years and the mean age at bilateral breast cancer diagnosis was 43 years.

The average time it took for development of bilateral breast cancer was 2 years (range of 0-11 years). Six patients (28.6%) had synchronous tumors while fifteen patients (71.4%) had metachronous tumors

In terms of comorbidities, none of the cases recorded had family history of breast malignancy or other form of malignancies, none were diabetic and none were diagnosed with retroviral disease. 14.3% of the cases were on management for hypertension.

In terms of pathology, invasive ductal carcinoma was the only carcinoma found with a single case of malignant phylloides sarcoma. These results were replicated in the contra lateral tumor pathology with similar frequencies. There was no case of invasive lobular carcinoma noted.

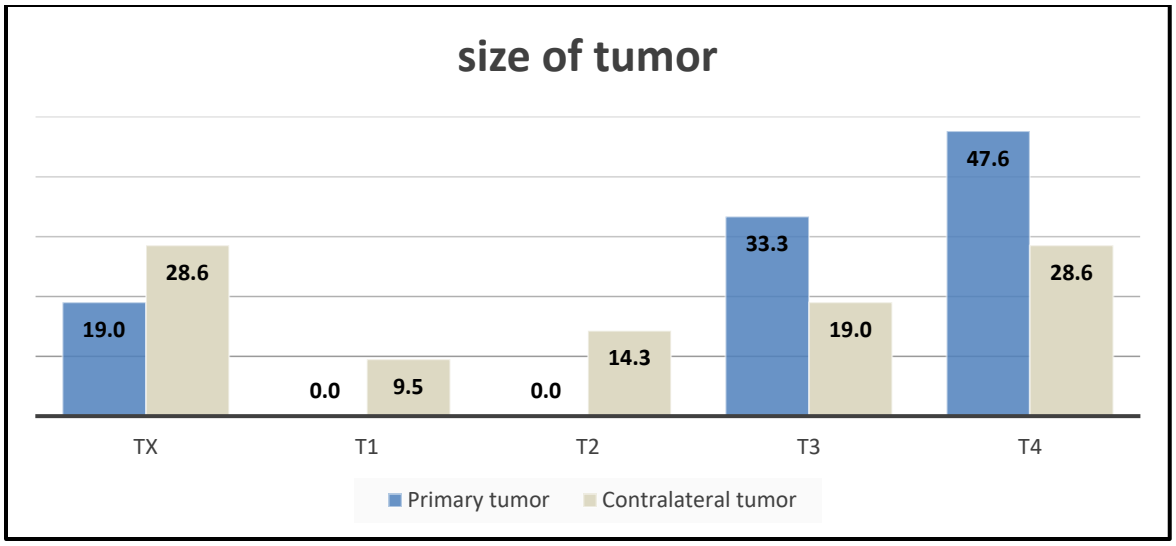


Figure 3: Tumor Size

The primary tumor size had a direct correlation with development of contra lateral breast malignancy. 33.3% of primary tumors were more than 5cm in widest dimension and 47.6% were T4 tumors. This corresponded to 19% and 28.6% T3 and T4 tumors respectively in the contra lateral breast. Some of the tumors could not be assessed (Tx) due to missing records or inaccurate examination findings.

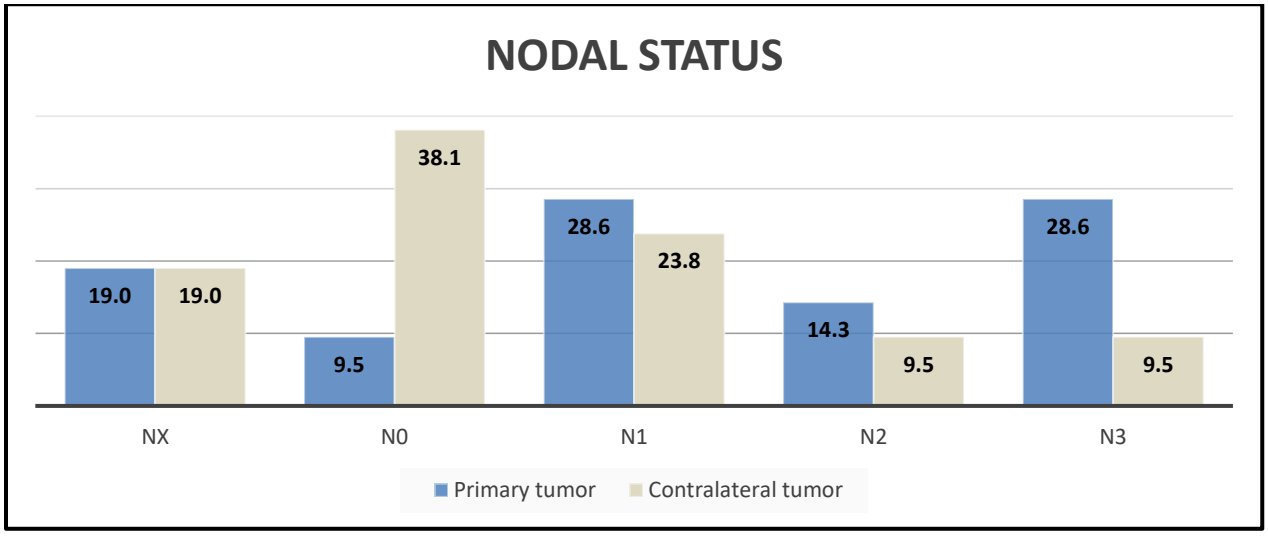


Figure 4: Nodal status

Nodal status did not seem to have a direct correlation with development of contra lateral breast malignancy with bilateral breast cancer diagnosis being made irrespective of nodal status of the primary malignancy.

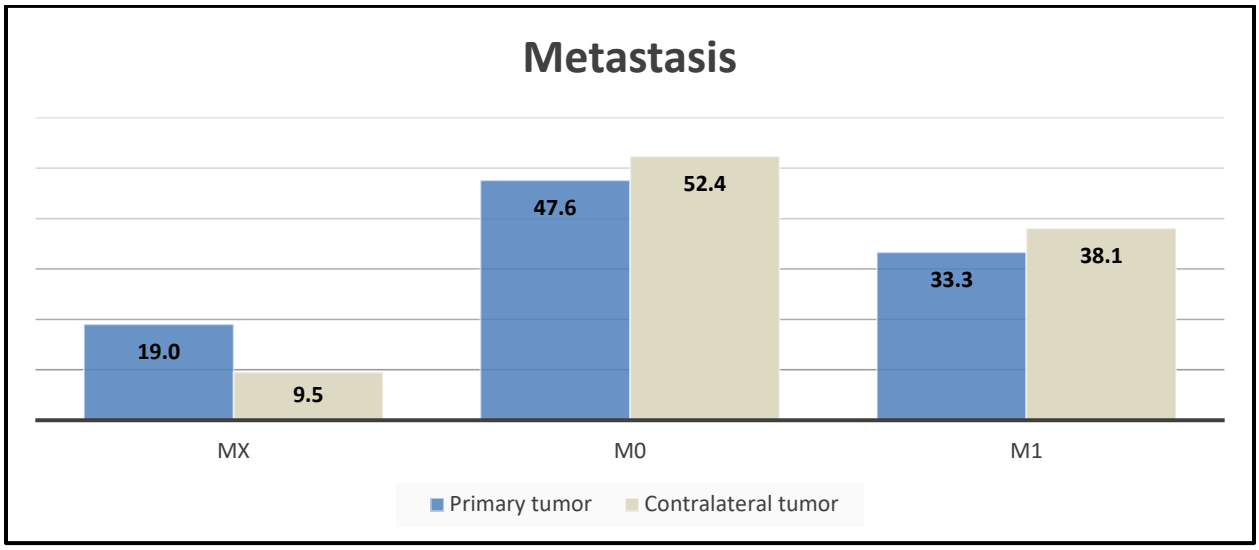


Figure 5: Metastasis

When assessing metastasis, 47.6% of the patients at the time of diagnosis of the primary tumor had no distant metastasis compared to 52.4 % of patients who developed bilateral breast cancer. 33.3% of unilateral breast cancer patients had distant metastasis to other organs apart from the other breast at time of diagnosis compared to 38.1% of patients with bilateral breast malignancies.

In terms of stage, patients who were at stage four at primary staging, had a significant chance of development of contra lateral malignancy with development of bilateral breast malignancy being seen in 61.9% of these patients.

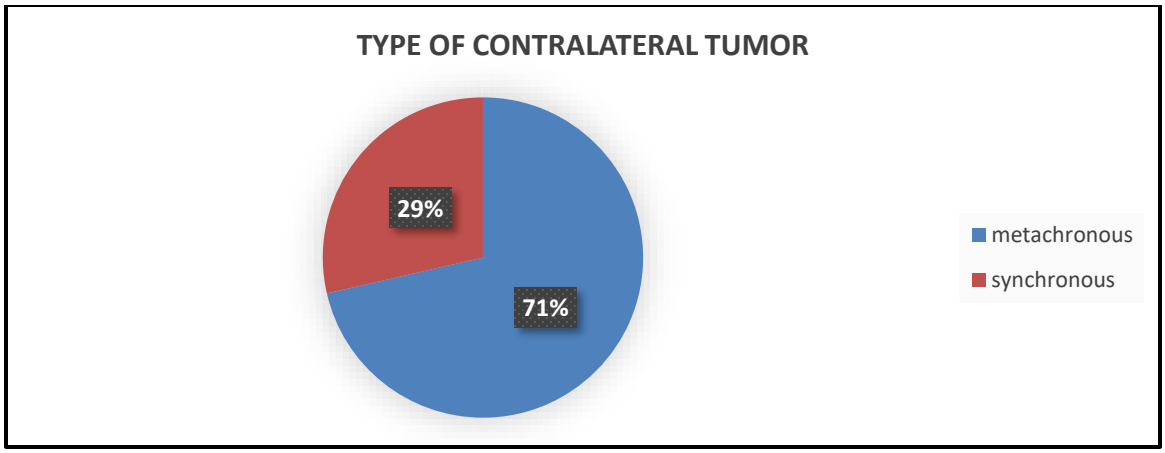


Figure 6: Type of contra lateral tumor

71% of contra lateral breast malignancies, developed after one year with only 29% of contra lateral breast malignancies occurring within the same year.

The immunohistological subtypes for all patients were similar both at primary diagnosis and at secondary diagnosis irrespective of the contralateral tumor being synchronous or metachronous.

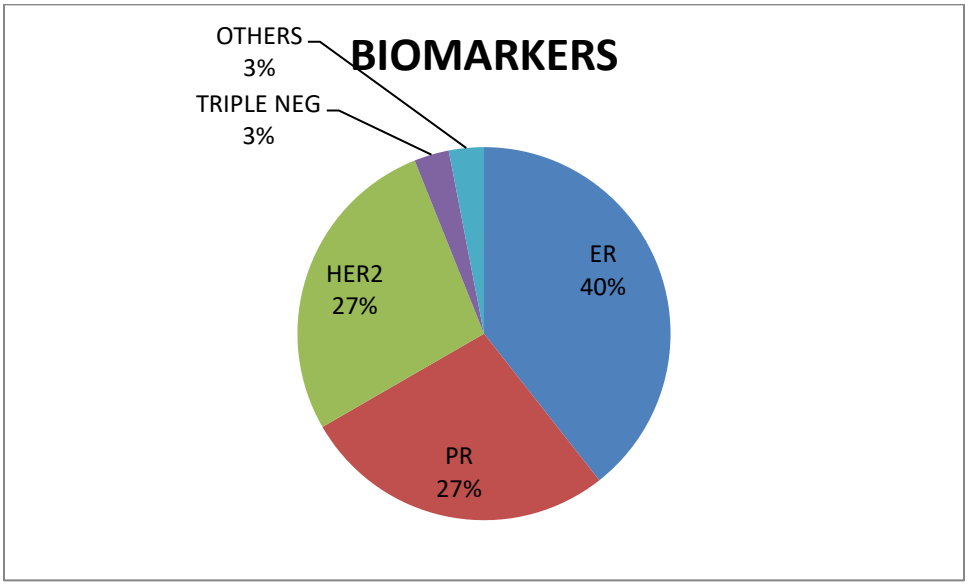


Figure 7: contra lateral breast tumor biomarker availability

The commonest receptor was ER (Estrogen receptor) at 40%, followed by PR (progesterone receptor) and HER 2(human epidermal growth factor receptor) at 27%,3% of these tumors lacked these receptors or were of a different phenotype.

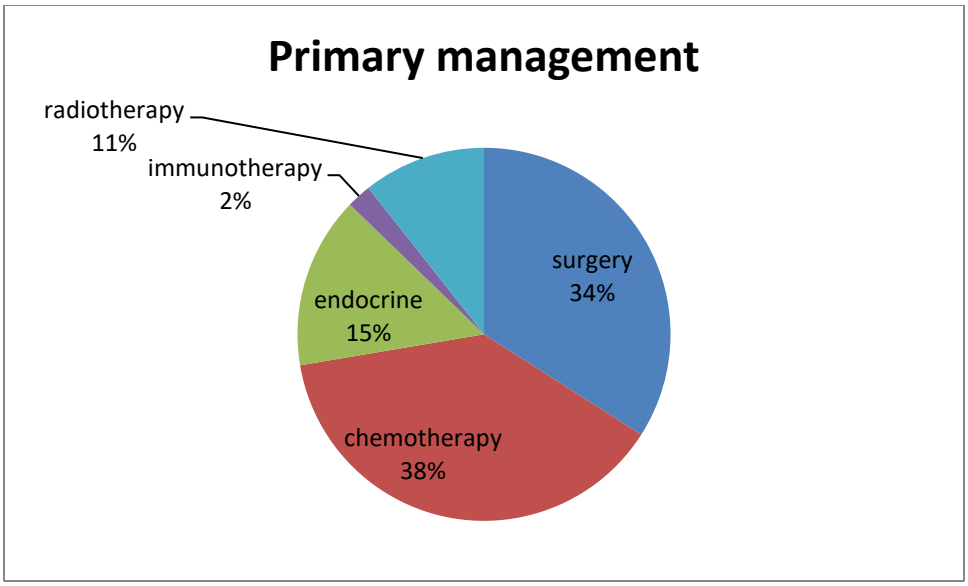


Figure 8: Management of Primary Breast Cancer

Amongst patients who developed bilateral breast cancer, 38% had received chemotherapy, 34% had been operated on, 15% had received endocrine treatment, 11% had received radiotherapy and 2% immunotherapy for management of their primary malignancy.

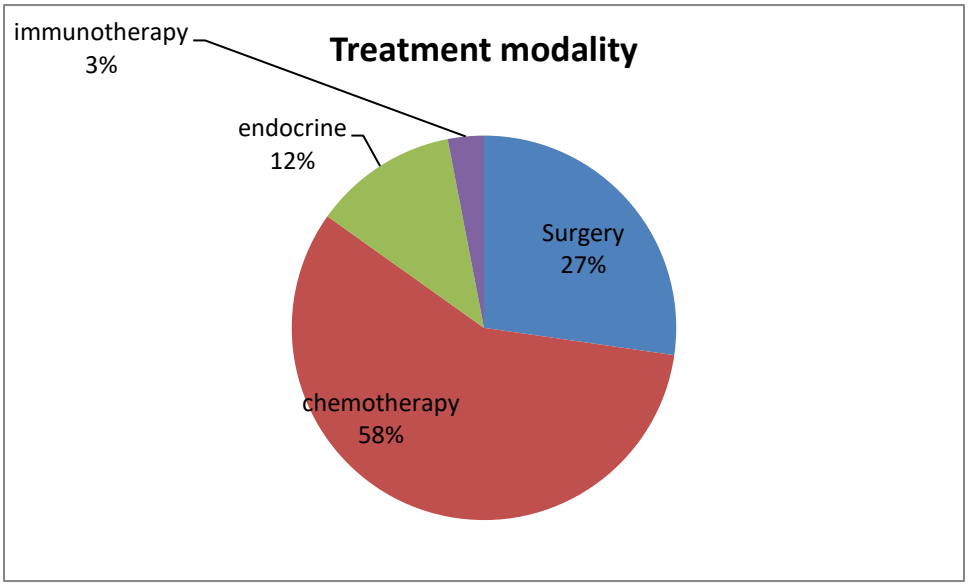


Figure 9: Management of bilateral breast cancer

Chemotherapy was the management commonly used in management of patients with bilateral breast malignancies at 58% with surgery done for the second breast in 27% of the patients and endocrine treatment for 12% of the patients. No patient received radiotherapy.

5.0 DISCUSSION

Bilateral breast cancer is a disease entity that has not been researched extensively in our set up. As quoted earlier in the literature review, few articles have delved into this topic.

Our incidence rate was seen to be similar to studies carried out in India (3) Sudan (4) China (5) and Korea (6). However higher incidence rates were seen with United Kingdom (7) and Australia (8) due to the different methodology involved. For the studies carried out in United Kingdom and Australia, patients were assessed from the whole country retrieving data from the registry banks unlike the other studies including ours which focused on a single centre.

From our study, risk factors that were associated with risk of developing bilateral breast cancer included female gender, ages less than fifty years, invasive ductal carcinoma histology, large primary tumor size of more than 5cm, advanced primary staging and primary mode of treatment. Breast cancer in the index breast, a positive family history of breast cancer, a first cancer diagnosis at a young age, and BRCA genetic mutations are some of the factors that had been found to facilitate bilateral breast cancer occurrence from previous studies. (2, 6, 7, 9, 13). These factors were similar to our study with the exception of a strong family history of breast malignancy and genetic testing was not carried out in this study. Absence of the association between family history of breast cancer and BiBc development in our set up can be attributed to the small number of patients discovered during this study hence a similar progressive study should be carried out in a larger scale and follow up of patients done for more than five years.

Ages between 40 and 50 years (range of 11-70 years) were noted to be high risk for development of bilateral breast cancer from our study. These findings are similar to other studies done on this subject (3,4,8,9) Most of the patients with this diagnosis have a genetic predisposition to these tumors(5) and hence once the primary tumor develops, it takes a short while for development of the secondary tumor, from our study it took two years (range of 0-11 years.) Dr. Kieran McCaul in his study on bilateral breast cancer and survival noted, women in their 40s and 50s have a long life expectancy as compared to women who develop primary tumors at a younger age and hence

this age group will have higher prevalence. He also found out that young women indeed have a higher chance of developing bilateral breast cancer but the incidence is confined to when they are young and as they age the incidence begins to reduce and it levels out by age 50.(8)

This study found out that metachronous tumors occur more frequently than synchronous tumors however correlating these findings with other studies proves difficult based on the time difference when describing these terms amongst different scientists. In some studies, BiBc diagnosed within three months of each other were regarded as synchronous (5) whereas in others if they occurred within six months(6,10) or even within one year(3,8,11,12), they were synchronous.

With respect to histopathology, invasive ductal carcinoma was the commonest type of carcinoma for both the primary tumor and the contra lateral tumor. This is similar to other studies(3,5–7,12) on this topic and could be due to the fact that invasive ductal carcinoma is more prevalent in patients than other types of breast cancers and hence detected more often. However Zhang et al the molecular study of this disease found out those women with lobular histology develop contra lateral breast cancer more frequently than ductal cells. (5)

Patients with bilateral breast carcinoma were noted to have a higher association with metastasis to other organs than the breast when compared to when the primary tumor developed. Involvement of other organs for Bibc was also noted to be higher than for unilateral tumors. This may be explained by changes in biology between the first tumor and the second tumor. The secondary cancer cells may have not been amenable to the primary treatment offered or may be remnant cells that have different cellular characteristics as found in the primary tumor(9)

When looking at tumor immunohistochemistry, we found that in all patients, both tumors demonstrated similar steroid biomarkers. These findings were also demonstrated by other studies (5,6,11). Hence this observation may actually place BiBc as a metastasis to the other breast and not as a new disease and hence different more aggressive management strategies need to be employed for these patients as soon as possible without much repeat in investigations previously carried out for the first tumor.

With regards to management, most patients who developed BiBc, initially received chemotherapy, surgery and endocrine therapies for management of the primary tumor.

Chemotherapy was used mostly for management of patients with BiBc. With relevance to the article on epidemiology of contra lateral breast cancer (14), there was no significant risk in development of Bibc after initial use of radiotherapy, chemotherapy or tamoxifen when managing the primary tumor. Progression to BiBc is independent from previous treatment administered for the primary tumor .(14,15). Perhaps the occurrence of BiBc signifies a metastatic primary tumor.

6.0 CONCLUSION

Bilateral breast malignancy is an uncommon entity in our setup occurring mostly in the fourth decade of life with an average diagnostic period of two years from time of primary breast cancer diagnosis. Risk factors include age, patients with stage three and four tumors and invasive ductal carcinoma diagnosis on pathology. Bilateral breast malignancies carry a higher risk of metastasis to other organs and close follow up is warranted. Since immunohistochemical markers appear to be similar between primary malignancy and the contra lateral malignancy, there needs to be a revision in terms of treatment as there is a chance that both tumors are share some histopathological aspects with contra lateral tumors being more aggressive as compared to primary tumors and time to treatment can be reduced as similar results have been demonstrated in terms of clinical pathological parameters and immunohistochemistry between primary breast tumors and contra lateral breast tumors.

7.0 RECOMMENDATIONS

Further studies need to be conducted in terms of:

1. Management strategies used in treatment of patients with unilateral breast cancer and what percentages of patients develop bilateral breast cancer with each strategy in our country?
2. Comparison of the tumor grade and tumor subtypes between the primary and contra lateral tumors, are they the same histologically?
3. Genetic markers that predispose to development of bilateral breast malignancies
4. Differences between synchronous tumors and metachronous tumors

5. Mortality and morbidity rates between unilateral breast cancer patients and bilateral breast cancer patients.
6. Long term prospective studies on Bilateral Breast Cancer clinicopathological characteristics and immunohistochemistry.

REFERENCES

1. Globocan 2020.*Kenya international Agency for research on cancer.* Available from https://gco.iarc.fr/today/data/factsheets/populations/404-kenya-fact-sheets.pdf.(Accessed 01 September 2021)

2. Reiner AS, Sisti J, John EM, Lynch CF, Brooks JD, Mellemkjær L, et al. Breast cancer family history and contralateral breast cancer risk in young women: an update from the women's environmental cancer and radiation epidemiology study. Journal of clinical oncology. 2018 May 20;36(15):1513.

3. Giardiello D, Steyerberg EW, Hauptmann M, Adank MA, Akdeniz D, Blomqvist C, et al. Prediction and clinical utility of a contralateral breast cancer risk model. Breast cancer research. 2019 Dec;21(1):1-3.

4. Kramer I, Hooning MJ, Mavaddat N, Hauptmann M, Keeman R, Steyerberg EW, et al. Breast cancer polygenic risk score and contralateral breast cancer risk. The American Journal of Human Genetics. 2020 Nov 5;107(5):837-48.

5. Mubarik S, Malik SS, Wang Z, Li C, Fawad M, Yu C. Recent insights into breast cancer incidence trends among four Asian countries using age-period-cohort model. Cancer management and research. 2019;11:8145.

6. Geurts YM, Witteveen A, Bretveld R, Poortmans PM, Sonke GS, Strobbe LJ, et al. Patterns and predictors of first and subsequent recurrence in women with early breast cancer. Breast cancer research and treatment. 2017 Oct;165(3):709-20.

7. Johnson RH, Anders CK, Litton JK, Ruddy KJ, Bleyer A. Breast cancer in adolescents and young adults. Pediatric blood & cancer. 2018 Dec;65(12):e27397.

8. Uyisenga JP, Butera Y, Debit A, Josse C, Ainhoa CC, Karinganire E, et al.Prevalence of histological characteristics of breast cancer in Rwanda in relation to age and tumor stages. Hormones and Cancer. 2020 Oct;11(5):240-9.

9. Kuchenbecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. Jama. 2017 Jun 20;317(23):2402-16.

10. Testa U, Castelli G, Pelosi E. Breast cancer: a molecularly heterogeneous disease needing subtype-specific treatments. Medical Sciences. 2020 Mar;8(1):18.

11. Qian X, Jia H, Zhang Y, Ma B, Qin G, Wu Z. Risk factors and prediction of second primary cancer in primary female non-metastatic breast cancer survivors. Aging (Albany NY). 2020 Oct 15;12(19):19628.

12. Balekouzou A, Yin P, Pamatika CM, Bishwajit G, Nambei SW, Djeintote M, et al. Epidemiology of breast cancer: retrospective study in the Central African Republic. B.M.C. Public Health. 2016 Dec;16(1):1-0.

13. Anwar SL, Prabowo D, Avanti WS, Dwianingsih EK, Harahap WA, Aryandono T. Clinical characteristics and the associated risk factors of the development of bilateral breast cancers: a case-control study. Annals of Medicine and Surgery. 2020 Dec 1;60:285-92.

14. Kotecha R, Tonse R, Rubens M, McDermott M, Odia Y, Appel H, et al. SYSTEMATIC REVIEW AND META-ANALYSIS OF BREAST CANCER BRAIN METASTASIS AND PRIMARY TUMOR RECEPTOR EXPRESSION DISCORDANCE. Neuro-oncology Advances. 2020 Aug;2(Suppl 2).

15. Dania V, Liu Y, Ademuyiwa F, Weber JD, Colditz GA. Associations of race and ethnicity with risk of developing invasive breast cancer after lobular carcinoma in situ. Breast Cancer Research. 2019 Dec;21(1):1-7.

16. Fadl AI, Hassan AM. Detection of Carcinoembryonic Antigen Expression among Sudanese Women with Invasive Ductal Carcinoma of the Breast in Bahri Teaching Hospital. African Journal of Medical Sciences. 2019;4(1).

17. Ramião NG, Martins PS, Rynkevic R, Fernandes AA, Barroso M, Santos DC. Biomechanical properties of breast tissue, a state-of-the-art review. Biomechanics and modeling in mechanobiology. 2016 Oct;15(5):1307-23.

18. Dia JM, Touré M, Yao I, Bohoussou E, Saki C, Oyelade M, et al. Breast cancers in young woman under 40 years in sub-Saharan Africa: Experience of the Gynecology Department of the University and Hospital Center of Treichville (Abidjan—Cote d'Ivoire). Journal of Cancer Therapy. 2017 Aug 3;8(08):714.

19. Badowska-Kozakiewicz AM, Budzik MP. Immunohistochemical characteristics of basal-like breast cancer. Contemporary Oncology. 2016;20(6):436.

20. Cubasch H, Dickens C, Joffe M, Duarte R, Murugan N, Chih MT, et al. Breast cancer survival in Soweto, Johannesburg, South Africa: a receptor-defined cohort of women diagnosed from 2009 to 11. Cancer epidemiology. 2018 Feb 1;52:120-7.

21. Githinji P. *Histopathology Reporting and Biomarker Testing of Invasive Breast Cancer at Kenyatta National Hospital: an Audit of the Synoptic Reports and Determination of Er/pr/her2 Receptor Profiles*. 2019.

22. Krishnappa R, Chikaraddi S B, Deshmane V. Primary synchronous bilateral breast cancer.2014. Indian J Cancer.htm.

ANNEXES/ APPENDICES
DATA COLLECTION SHEET

1. **Demographics**

a. Age at primary diagnosis

b. Age at contralateral diagnosis

c. Sex male female

d. Family history of breast cancer?

Comorbidities

a. Hypertension yes no

b. Diabetes mellitus yes no

c. H.I.V. yes no

d. Others

2. **Histology**

a. Invasive ductal carcinoma (primary)

b. Invasive lobular carcinoma (primary)

c. Others (primary)

d. Tumor Size (primary) in centimeters

e. Nodal status (primary)

f. Stage at primary tumor

g. Invasive ductal carcinoma (contralateral)

h. Invasive lobular carcinoma (contralateral)

i. Others (contralateral)

j. Tumor size in centimeters (contralateral)

k. Nodal status (contralateral)

l. Stage of contralateral tumor

m. Synchronous contralateral tumor Metachronous contralateral tumor

n. Time interval of contralateral tumor (months)

3. Immunohistochemistry

a. Primary tumor

ER positive negative

PR positive negative

HER 2 positive negative

KI-67

b. contralateral tumor

ER positive negative

PR positive negative

HER 2 positive negative

KI-67

4. Management (primary tumor)

a. Surgery Mastectomy breast conserving surgery

b. Chemotherapy

c. Radiotherapy ☐

d. Endocrine ☐

e. Immunotherapy ☐

f. Others (specify) ☐

5. Management (contralateral)

a. Surgery Mastectomy ☐ Breast-conserving surgery ☐

b. Chemotherapy ☐

c. Radiotherapy ☐

d. Endocrine ☐

e. Immunotherapy ☐

f. Others (specify) ☐