A COMPARISON BETWEEN DIGITAL BREAST TOMOSYNTHESIS AND ULTRASOUND IN THE CHARACTERIZATION OF MAMMOGRAPHIC BREAST LESIONS USING HISTOPATHOLOGY AS THE GOLD STANDARD AT KENYATTA NATIONAL HOSPITAL

A CROSS-SECTIONAL MATCHED PAIRS DESIGN

Submitted by:

NAAILA BALARAMAN KUPPUSWAMY

H58/6159/2017

A research dissertation submitted in partial fulfillment for the degree of Master of Medicine (MMED) in Diagnostic Radiology, University of Nairobi

2022

DECLARATION

By submitting this research dissertation, I declare that the entirety of the work contained therein, is my original work and that it has not previously, in its entirety or part, been submitted in any university for the award of a degree.

Signature: _____ **Date:** 16/3/2022

Naaila Balaraman Kuppuswamy

APPROVAL BY SUPERVISORS

This dissertation has been submitted with the approval of the following supervisors,

Signature: _____ **Date:** 28/3/2021

Dr. Gladys Mwango

Consultant Radiologist and Senior Lecturer,

Department of Diagnostic Imaging and Radiation Medicine,

Faculty of Health Sciences.

Signature: _____ **Date:** 26/3/2021

Dr. Beatrice Mugi

Consultant Radiologist,

Department of Diagnostic Radiology,

Kenyatta National Hospital.

CERTIFICATE OF AUTHENTICITY

This is to certify that this dissertation is the original work of DR. NAAILA BALARAMAN KUPPUSWAMY a Master of Medicine Student in the Department of Diagnostic Imaging and Radiation Medicine, University of Nairobi, under the guidance and supervision of the aforementioned supervisors. This dissertation has not been presented in this or any other University for the award of a degree.

Signature: _____ **Date:** 28/3/2021

DR.GLADYS MWANGO

Chairperson, Department of Diagnostic Imaging and Radiation Medicine,
Faculty of Health Sciences, University of Nairobi.

2D	2- Dimensional
3D	3-Dimensional
ACR	American College of Radiology
BI-RADS	Breast Imaging Reporting and Data System
CC	Craniocaudal
DBT	Digital Breast Tomosynthesis
DM	Digital Mammography
FFDM	Full-field digital mammography
ERC	Ethical Research Committee
KNH	Kenyatta National Hospital
LLIQ	Left lower inner quadrant
LLOQ	Left lower outer quadrant
LMP	Last menstrual period
LUIQ	Left upper inner quadrant
LUOQ	Left upper outer quadrant
MD	Mammographic density
MLO	Mediolateral Oblique
RLIQ	Right lower inner quadrant
RLOQ	Right lower outer quadrant
RUIQ	Right upper inner quadrant
RUOQ	Right upper outer quadrant
UoN	University of Nairobi
US	Ultrasound
ABUS	Automated breast ultrasound
PACS	Picture archiving and communication system
FSM	Film screen mammography
PPE	Personal protective equipment

DEFINITION OF TERMINOLOGIES

Mammography: This is an imaging technique that uses low-energy x-ray photons to obtain 2D images of the breast.

Screening mammography: Mammography carried out to detect cancer in asymptomatic clients.

Diagnostic mammography: Mammography performed in symptomatic clients who have signs and symptoms of breast disease.

Digital mammography: Also known as full-field digital mammography, is a mammography system in which the x-ray film is replaced by solid-state detectors that convert x-rays into electrical signals. These electrical signals are used to produce breast images that can be visualized on the computer screen and can be easily shared electronically.

Digital breast tomosynthesis: This is a 3D imaging software provided for in the digital mammography machine. Using the same x-ray source as the digital mammography, a DBT unit moves at an arc angle of 15-45 degrees while taking a series of 10-20 images. These images are then reconstructed to create imaging similar to CT in which a series of thin slices about 1mm are assembled to create a 3-D reconstruction of the breast.

Mass: Space occupying 3D lesion seen in two different projections and has an outwardly convex margin.

Architectural distortion: Radiating linear densities emerging from a central point with no definitive visible mass.

Focal asymmetry: This is a lesion seen on two mammographic projections but does not have outwardly convex margins.

Acoustic enhancement: Refers to a column of increased echogenicity posterior to a mass. It is one of the characteristics of a cyst in breast ultrasound.

Acoustic shadowing: Result when tissues absorb or reflect the incident ultrasound beam. It appears as dark bands along the projected course of the beam and is associated with fibrosis, such as from a neoplastic desmoplastic reaction or surgical scar.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Introduction: Breast cancer ranks second after lung cancer in both sexes globally, and the commonest occurring cancer in women worldwide. Africa has been recorded as having the highest age-standardized breast cancer mortality rate globally with sub-Saharan Africa reporting the highest incidence rates. Mammography is used for both screening and diagnosis of breast malignancy worldwide with high sensitivity in fatty breasts (80-98%), but limited in depicting lesions in dense breasts (30-48% sensitivity). Combined mammography and breast ultrasound imaging have a 100% sensitivity in depicting lesions in dense breasts. Digital breast tomosynthesis (DBT) eliminates glandular tissue superposition in dense breasts allowing easier detection and characterization of breast lesions. The diagnostic performance of DBT to characterize mammographic lesions, compared to that of breast US has not been well documented.

Objective: To compare the diagnostic accuracy of Digital Breast Tomosynthesis to that of Ultrasound as adjuncts to mammography in the characterization of mammographic breast lesions at the Kenyatta National Hospital using histopathology as the gold standard.

Methodology: A cross-sectional matched pairs design was used for a 6 month study period. The study sites were The Radiology department of the Kenyatta National Hospital and the Department of Diagnostic Imaging and Radiation Medicine at The University of Nairobi. The sample size was 92. The study population was clients who sought screening and diagnostic mammography services and with lesions detected on digital mammograms. The collected data were checked for completeness and accuracy before being entered into Microsoft Excel for analysis using STATA software version 15. The diagnostic accuracy of DBT and ultrasound was determined using cross-tabulation. Fisher's exact test and Chi-square were used to compare the diagnostic performance of DBT and ultrasound.

Results: Of the 92 female participants, the majority were aged between 50-59. 82 were symptomatic with a majority (75.6%) having breast lumps. On histopathology, 73 patients had malignant lesions, the commonest malignancy being invasive ductal carcinoma in 70 women, with fibroadenoma the commonest benign lesion in 14 patients. The sensitivity and specificity of the DBT were 95.8% and 80.0% respectively, with a Positive Predictive value of 94.5% and a Negative Predictive Value of 84.2%. The diagnostic accuracy was 92.4%. For breast US, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were 98.6%, 78.9%, 94.76%, 93.8%, and 94.6% respectively. The p-

values comparing sensitivity and specificity for DBT and US were 0.251 and 0.854 respectively (not statistically significant).

Conclusion: The diagnostic accuracy of DBT compared to that of breast ultrasound in the characterization of breast lesions depicted on mammography was found to be similar.

Recommendations: Correlative US or DBT to be done for patients in the same sitting for inconclusive findings on mammography to save the patients cost and time.

Key Words: Tomosynthesis, Ultrasound, Diagnostic performance,

CHAPTER 1: INTRODUCTION

1.1 Background of the Study

Amongst the commonest cancers occurring globally, breast cancer is ranked second with an incidence of 11.6% (1). In women, it is the commonest occurring cancer. It accounted for 17.5 million cases of cancer in 2015 with a death toll of 9 million in the same year (2). Africa was stated to have the highest age-standardized breast cancer mortality rate on a global scale with sub-Saharan Africa reporting the highest incidence rates (3). According to GLOBOCAN 2018 breast cancer in Kenya had the highest reported incidence rates in both sexes standing at 5985 cases (12.5%). In women, this takes up 20.9 % of all new cancer cases (1).

In women aged 40-79 years, the specificity and sensitivity of mammography screening during breast cancer diagnosis ranges from 92-98% and 81-87% respectively. Its detection breast cancer detection rate is approximately 4-5 per 1000 examinations (4). However, the overall sensitivity of mammography is limited by dense breast tissue and in dense fibro glandular tissue; underlying cancer can be easily masked. Overall, among women with dense breasts, sensitivity drops to between 47.8% and 64.4%. Moreover, increased breast density confers a greater risk of developing cancer of the breast (5). The specificity is also limited by the presence of dense fibro glandular tissue which can mimic tumors (6).

The Digital Breast Tomosynthesis (DBT) imaging procedure generates multiple images of the breast by angling the X-ray tube in different planes while the breast is at a fixed position and thus enabling reconstruction of 3D images that are easier to interpret (7). DBT has demonstrated better characterization of breast cancer and normal structures. DBT reduces the summation effect caused by overlapping of breast tissue, which can resemble cancer of the breast thus giving false positives. It also provides better detail of non-calcified mammographic features seen in breast cancer, localizes breast lesions better, and aids in the determination of the mammographic extent of disease in women with known or suspected cancer of the breast (7). DBT also has its disadvantages. It can miss or even misinterpret some of the malignancies due to its limited capability of visualization of microcalcification and results in an increased radiation dose when combined with DM. The increased dose is still lower than the maximum acceptable dose of 3mGY/view according to the Food and Drug Administration, safety limits(8).

Breast ultrasonography has also proven an effective supplemental tool for the evaluation of areas of abnormality seen on mammography. It is readily available and affordable. To add to that, it is also well tolerated by patients (9). Breast ultrasonography has been recommended as a supplement to mammography for patients whose probability of developing breast cancer is high, pregnant women, and patients unable to do mammography. It is a more sensitive form of imaging but unfortunately at the expense of reduced specificity and increased biopsy rates(10). It is also highly user-dependent. This means that it heavily relies on the operator's experience and expertise for the validity of the result (11). Ultrasonography has played an important role as a complementary screening technique in women with dense breasts with increased cancer detection rates and reduced false-positive results (12).

The purpose of this study is to compare the diagnostic accuracy of Digital Breast Tomosynthesis to that of Ultrasound as adjuncts to mammography in characterizing mammographic lesions using histopathology as the gold standard.

No Kenyan studies have been done before comparing the accuracy of the two modalities as adjuncts to 2D mammography. Globally, there is still limited data on the same. From this study, the Radiology department of Kenyatta National Hospital may be in a better position to determine which imaging strategy to adopt using local data thereby informing on the current practice.

CHAPTER 2: LITERATURE REVIEW

2.1 Screening and Diagnosis of Breast Cancer

For women between the ages of 40-74 who actively participate in screening every year, breast cancer mortalities have been reduced by 40 %(13). With the correct approach, the breast cancer cases are fewer or rather over-diagnosis accounts for 10%. False positives are found in about 10% of screened patients, in which case 80% of these patients their cases are resolved by additional imaging and 10% with breast biopsy (13).

With the advancement in technology, DBT and breast ultrasonography minimize the false negative rate experiences with mammography when patients have dense breast tissue(13). The current recommendation for annual mammographic screening by ACR is for women aged 40 years who exhibit an average risk of developing breast cancer. Moreover, women aged below 40 years but who have predictors for breast cancer (for instance family history) may need earlier and intense screening, as they bear an equivalent risk to that of a woman with average risk (14).

2.2 Factors Influencing the Screening and Diagnosis of Breast Cancer

Several studies have been done citing factors influencing early detection of breast cancer through screening and diagnostic procedures. Inadequate knowledge on prevention, causes, and diagnoses of breast cancer was one main obstacle in breast cancer health behavior. A large proportion of participants were unaware of the different screening methods and the fact that breast cancer premalignant lesions can be self-detected on self-breast examination and had limited access to health care. Poor income also negatively affected transport to facilities as well as the payment costs of the screening method, primarily mammography. In sub-Saharan Africa, in several countries, breast cancer is rated high among the leading causes of cancer-related mortality and morbidity amongst women. This is suspected to be due to the low-income setting in most of these countries. Geographical location, specifically rural setting, also plays a role in limiting early screening and detection of breast malignancy (15–17).

In Kenya, breast cancer leads among the commonest cancer accounting for 23 percent of all cancers (34/100,000). WHO has recommended that early screening for breast cancer should be a priority in high prevalence areas to lower mortality and morbidity. Mammography was recommended as the most proficient technique for early diagnosis, and subsequent treatment of

breast cancer cases dues to its efficacy, cost-effectiveness, and ease of administration in low resource areas (17).

In 2018, breast cancer screening was low in Kenya at just 5%. This was influenced by several factors. The low education level of women created a significant knowledge gap on breast cancer screening and cancer in general in the country. Lack of sufficient knowledge and or awareness on breast cancer screening programs prevented the women who were at risk of the disease from identifying early signs and hence do not attend screening programs.

Religious background, marital and socioeconomic status were contributing factors. Unmarried women were less likely to have the recommended ANC contacts during antenatal care compared to married women and were also identified as predictors for the avoidance of breast cancer screening in urban settings.

Muslim women particularly in the Somali community with their norms did not undergo breast cancer screening especially if it was being done by male doctors. On socio-economic status, lack of resources would mean no access to a healthcare facility for the women to have breast screening performed, hence impact negatively on early detection of breast cancer (17).

2.3 Risk Factors of Breast Cancer

Various factors have been associated with a higher risk of developing breast cancer, which mainly includes age, hereditary/family history, oral contraceptive use, nulliparity, late parity, and genetic mutations. About 5-10% of cases of breast cancer have a genetic predisposition. Mutations of the BRCA 2 and BRCA 1 genes, for instance, are widely reported. In BRCA 1 carriers, the risk (lifetime) for breast cancer is about 50-85% and nearly 45% risk among BRCA 2 carriers. The CHEK2 (Li-Fraumeni syndrome), TP53, and, PTEN (Cowden and Bannayan-Riley-Ruvalcaba syndromes) are lesser-known gene mutations linked to breast cancer (18).

Despite an absence of genetic mutation, a strong family history especially first-degree relatives increases the probability of women developing breast cancer over their lifetime (18). Women with a familial history of breast cancer are at an increased risk of recurrence. From a meta-analysis of the data of 10801 women in 2018, Monticciolo and colleagues reported a 10-year breast cancer recurrence rate of women who underwent breast-conserving therapy to be 19.3%. Over a 15 year follow-up, the death rate of women who underwent therapy was 21.4% was (18).

The presence of high mammographic dense breasts, which presents as increased parenchymal breast tissue and less fatty adipose tissue, has been identified as a predisposing factor for breast cancer (19). Overall, among women with heterogeneously dense breasts, the risk of developing breast cancer is approximately 20% higher compared to average women. Those with extremely dense breasts are 2.1 times more at risk of developing breast cancer compared with the average woman. The sensitivity of mammography reduces with an increase in the density of breasts, mainly due to the superimposition of overlapping dense radiopaque tissue on the underlying cancer cell of breasts when two-dimensional imaging is done on the three-dimensional breast (20).

Chest wall radiation for the treatment of childhood cancer has been identified as a risk factor for breast cancer development. In a study of average-risk women in 2018, women with a history of mantle or chest wall radiation for Hodgkin's lymphoma at a young age had a statistically and clinically significant higher risk of breast cancer beginning approximately eight years following completion of radiotherapy (18).

2.4 The Role of Various Breast Imaging Modalities

Breast cancer remains the leading cause of cancer-related deaths in women worldwide with developing countries affected the most where many present with advanced disease(13). Early detection is, therefore, crucial to improving breast cancer outcomes and survival.

The imaging modality employed as both a screening and a diagnostic tool for breast cancer is mammography. Nevertheless, the appearance of tissue overlap on mammograms is a limitation to the interpretation of images in women with dense breasts. Digital breast tomosynthesis (DBT), a 3D image-segmented evaluation procedure, ameliorates this problem by reducing or eliminating this tissue overlap. Another important diagnostic adjunct to mammography in detecting a solid mass or an area of architectural distortion as well as identifying a cystic mass is the Breast ultrasound (21).

Breast imaging modalities are regularly being developed to diagnose breast cancer early. Some of these modalities are used for screening, others for diagnostic uses, and others for adjunct evaluation of breast lesions (22).

2.4.1 Mammography

Mammography is the benchmark modality for imaging the breast, it is used as the primary screening and diagnostic tool (23,24).

In a study done by Emlik et al, this technique alone gives an 80-90% sensitivity for screening with regards to fatty breasts. Unfortunately, it is a limited technique when screening for women with dense breasts with low sensitivity (30-48%) (12)

Almost 10-15% of breast cancers are undetectable on mammograms denoting that a negative mammogram examination does not necessarily imply a lack of cancer, especially when patients have a suspicious palpable mass. Consequently, the development of other imaging modalities that can corroborate or reject the findings of initial mammogram findings is on course. These adjunct modalities can help to characterize the mammographic lesions as benign or malignant, in a specific and sensitive manner and enable the singling of lesions for biopsies accurately (24).

2.4.2 Digital breast tomosynthesis

Tomosynthesis/3D mammography, a recent technological advancement in Digital mammography, develops three-dimensional images of breasts from multiple low-dose images along an arch of the breast per view. As the X-ray tube is maneuvered around 1 degree in a 15-50-degree arch per low dose image, the breast tissue (compressed) remains stationary, improving accuracy. Then, the radiographer projects the images as 1mm thick cross-sectional slides, potentially overcoming the limitation of DM that arises from an overlap of pathological and normal tissues during standard two-dimensional (2D) breast projections (20,(9). Detection and characterization of lesions are therefore easier with this technique(12). Therefore, can improve visibility of the regions of architectural distortion and masses, resulting in more accurate breast imaging report and BI-RADS data system classification and improved discrimination between malignant and benign lesions. The visualization of Mammographic findings is illustrated more clearly in tomographic images, which improves BI-RADS categorization further (26).

Evidence suggests that combining digital tomosynthesis imaging with two-dimensional (2D) conventional mammograms could increase the detection rate for breast cancer and thus lower the incidence of false-positive recalls during screening (26).

Recent reviews have illustrated with evidence that when DBT is together with digital mammography there is an increment to breast cancer detection rate be it in screening or diagnostic settings (range increment of 0.5 – 2.7/1000 screens) (27).

Mariscotti et al, in 2016 conducted a multi-reader study on DBT as an adjunct to DM for detection and characterization of Invasive Lobular Cancers (ILC). It was ascertained that, when the two modalities were combined, mammographic accuracy in the depiction of ILCs was immensely improved (85% sensitivity) compared to DM alone (70% sensitivity). Thus, the characterization of the extent of the disease was significantly enhanced(27).

2.4.3 Breast ultrasound

Breast ultrasound is a major component of the diagnostic evaluation of breast lesions. Among youth ages <30 years, it is commonly used to examine palpable abnormalities. It is also routinely used to characterize mammographic abnormalities further as either a solid or a cyst and therefore provides direction for image-guided breast interventions (28).

Real-time scanning enables a thorough evaluation of breast lesions as well as detailed lesion analysis than analyzing static images on workstations. It may be difficult to capture irregular, subtle or distinct margins, architectural distortions, and artifacts on static images. Scanning in real-time permits the assessment of the location, mobility, and relationship of lesions and their adjacent structures and direct assessment of palpable lesions and other clinical findings(29).

Targeted breast ultrasound synergizes the efficacy of mammography during the characterization of masses and is the next examination performed for the same, as per the ACR appropriateness criteria. However, for the technique to deliver it is crucial to establish the depth and location of the mass identified via mammography and ensure that the breast imaging with the US is the same area. If a mass depicted by the US is thought to correlate to one identified by mammography, then its shape, size, surrounding tissue composition, and location should correlate between the two techniques (28).

In 2019, Mohamed et al investigated breast lesions in a hundred women with dense breasts using digital mammography and breast ultrasound as separate modalities. Then went on to combine both sonography and mammography for the same women. It was concluded that breast sonography was a major screening and diagnostic adjunct modality to mammography as it reduced the chances of missing the diagnosis of lesions in dense breasts. Breast ultrasound

combined with mammography showed a sensitivity of 100% while ultrasound alone was 90% and mammography 40% (30).

In a study done in 2017 assessing diagnostic performance of DBT and US and their effect on recall rates using histology as the gold reference standard, US was found to increase rates of cancer detection in dense breasts. Hence when used in conjunction with mammography it gave a 4.2- fold enhancement in cancer detection rate in 1000 women thereby preventing unnecessary biopsies on patients who didn't need it as well as eliminate false positives (12).

2.5 Digital breast tomosynthesis versus breast ultrasound as adjuncts to mammography

There is a limited number of published studies comparing the diagnostic performance of DBT compared to that of Breast ultrasound to characterize mammographic lesions. Kim et al, in 2015, did a comparison of the diagnostic performance of DBT to that of the breast US in distinguishing benign from malignant lesions depicted on digital mammography. In 119 patients with breast lesions, DBT illustrated 97.3% sensitivity and 44% specificity. The sensitivity and specificity of US were 98.7% and 39.4% respectively and concluded that the diagnostic performance of DBT was similar to that of ultrasound in characterizing lesions seen on a digital mammogram (9).

Won et al, in a retrospective study of 1103 patients, compared the diagnostic performance of digital breast tomosynthesis and breast ultrasound in women with dense breasts tissue with category 0 at digital mammography, revealed that the diagnostic performance of DBT is better than that of breast US for dense breast with category 0 and stressed that DBT lessens the false positive rate and short interval follow-up (31).

In 2017, Ganime and colleagues compared the diagnostic performance and screening recall rates of digital breast tomosynthesis and ultrasound added to digital mammography in category 0, which concluded that DBT reduced recall rates. DBT showed better diagnostic performance than breast for category 0 (12).

A study done in 2020, by Omnia M S et al, to investigate the diagnostic performance of DBT to that of breast sonography in the assessment of breast asymmetries depicted on digital mammography, revealed that DBT facilitates better detection of asymmetries while increasing cancer detection and decreasing the no of biopsies done. The study also confirmed that the breast US is more precise in the characterization of mammographic lesion underlying asymmetries compared to DBT (32).

2.6 Breast Imaging-reporting and data system (BI-RADS)

This is a risk assessment and quality assurance tool, globally accepted lexicon, and reporting schema for breast imaging founded by the American College of Radiology. It is a standardized method employed in reporting breast ultrasound, mammography as well as Magnetic Resonance Imaging (MRI)(33). It describes lesion contour to be the most discriminating morphological feature between benign and malignant masses. Benign lesions are usually well-circumscribed while malignant lesions have irregular margins. Nevertheless, some malignant masses owing to specific histological features may appear benign (circumscribed) on mammography. It is thereby imperative to correlate histological results with imaging data thus eliminating the failure to recognize an underlying malignancy (34).

BI-RADS Final Assessment categories

	Category	Management	Likelihood of cancer
0	Need additional imaging or prior examinations	Recall for additional imaging and/or await prior examination	n/a
1	Negative	Routine screening	Essentially 0%
2	Benign	Routine screening	Essentially 0%
3	Probably Benign	Short interval-follow-up (6 months) or continued	>0% but ≤2%
4	Suspicious	Tissue diagnosis	4a. low suspicious for malignancy (>2% to ≤10%) 4b. moderate suspicion for malignancy (>10% to ≤ 50%) 4c. high suspicion for malignancy (>50% to <95%)
5	Highly suggestive of malignancy	Tissue diagnosis	≥95%
6	Known biopsy-proven.	Surgical excision when clinical appropriate	n/a

Image courtesy of ACR BI-RADS Atlas, 5th edition.

Mammography Lexicon				Ultrasound Lexicon		
Breast composition	A. entirely fatty B. scattered areas of fibroglandular density C. heterogeneously dense, which may obscure masses D. extremely dense, which lowers sensitivity			**Breast composition**	a. homogeneous - fat b. homogeneous - fibroglandular c. heterogeneous	
Mass	**shape**	oval - round - irregular		**Mass**	**shape**	oval - round - irregular
	margin	circumscribed - obscured - microlobulated - indistinct - spiculated			**margin**	Circumscribed ***or*** Not-circumscribed: indistinct, angular, microlobulated, spiculated
	density	fat - low - equal - high			**orienta-tion**	parallel - not parallel
Asymmetry	asymmetry - global - focal - developing				**echo pattern**	anechoic - hyperechoic - complex cystic/solid hypoechoic - isoechoic - heterogeneous
Architectural distortion	distorted parenchyma with no visible mass				**posterior features**	no features - enhancement - shadowing - combined pattern
Calcifications	**morpho-logy**	typically benign		**Calcifications**	in mass - outside mass - intraductal	
		suspi-cious	1. amorphous 2. coarse heterogeneous 3. fine pleiomorphic 4. fine linear or fine linear branching	**Associated features**	architectural distortion - duct changes - skin thickening - skin retraction - edema - vascularity (absent, internal, rim) - elasticity	
	distribu-tion	diffuse - regional - grouped - linear - segmental		**Special cases** *(cases with a unique diagnosis)*	simple cyst - clustered microcysts - complicated cyst - mass in or on skin - foreign body (including implants) - intramammary lymph node - AVM - Mondor disease - postsurgical fluid collection - fat necrosis	
Associated features	skin retraction - nipple retraction - skin thickening - trabecular thickening - axillary adenopathy - architectural distortion - calcifications					

Adopted from ACR BI-RADS Atlas 5th Edition.

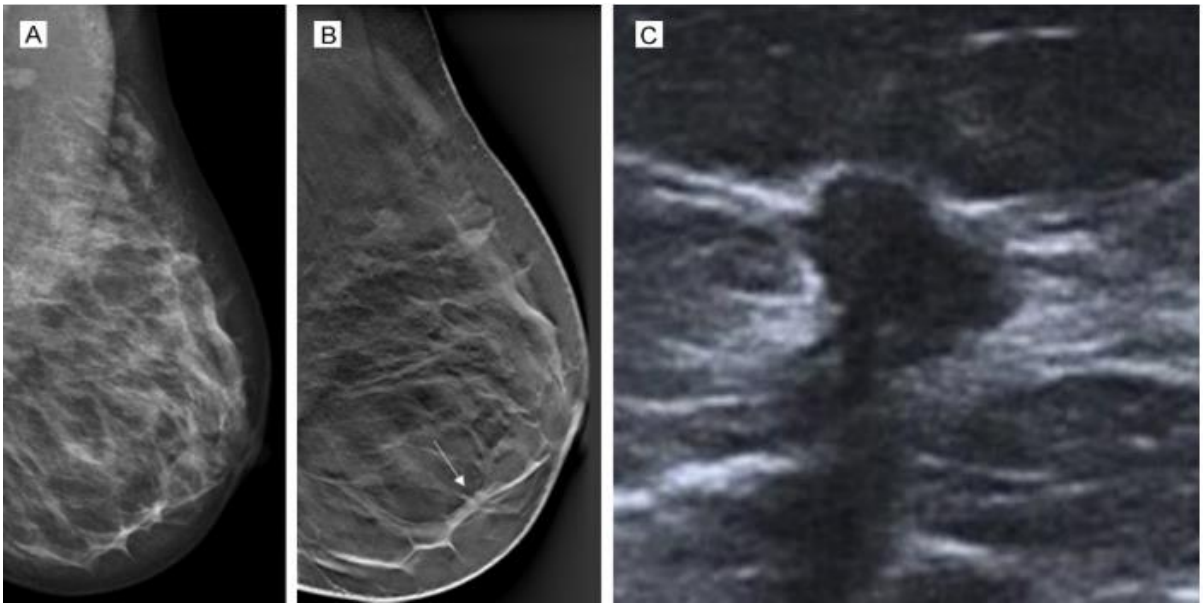


Figure 1. Craniocaudal digital mammography view (A) illustrates heterogeneously dense breasts. On craniocaudal digital breast tomosynthesis (B), a spiculated mass (arrow) was seen in the left breast. On ultrasound (C), a hypoechoic mass with irregular shape was detected and assessed as BIRADS 4C. Histology was done and revealed invasive ductal carcinoma (retrieved from Emlik et al., 2017)

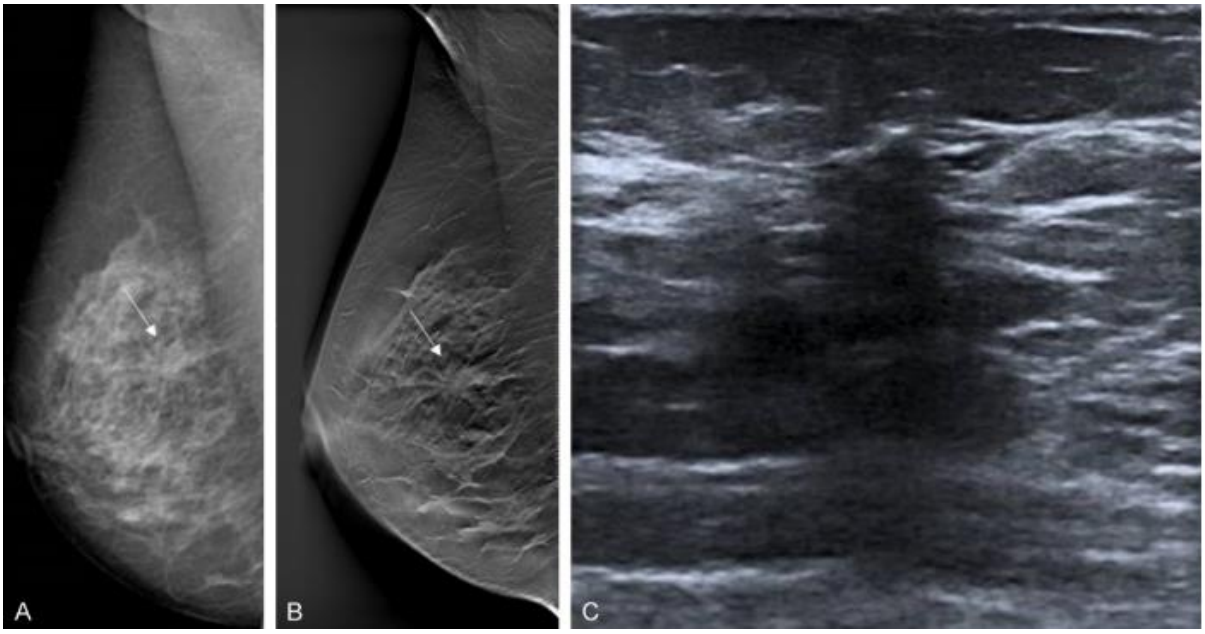


Figure 2. Mediolateral oblique digital mammography view (A) shows structural distortion (arrow) on the heterogeneously dense breast. On digital breast tomosynthesis (B), A spiculated mass (arrow) was detected at the center of the right breast and assessed as category 5. On ultrasound (c), a hypoechoic area with blurred contours was observed and assessed as category 4B. The mass was confirmed as sclerotic tissue (retrieved from Emlik et al., 2017)

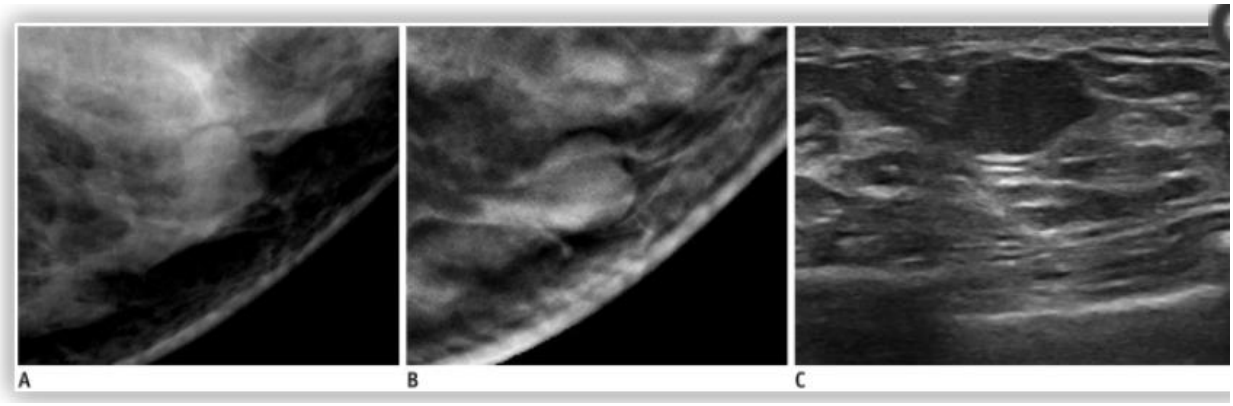
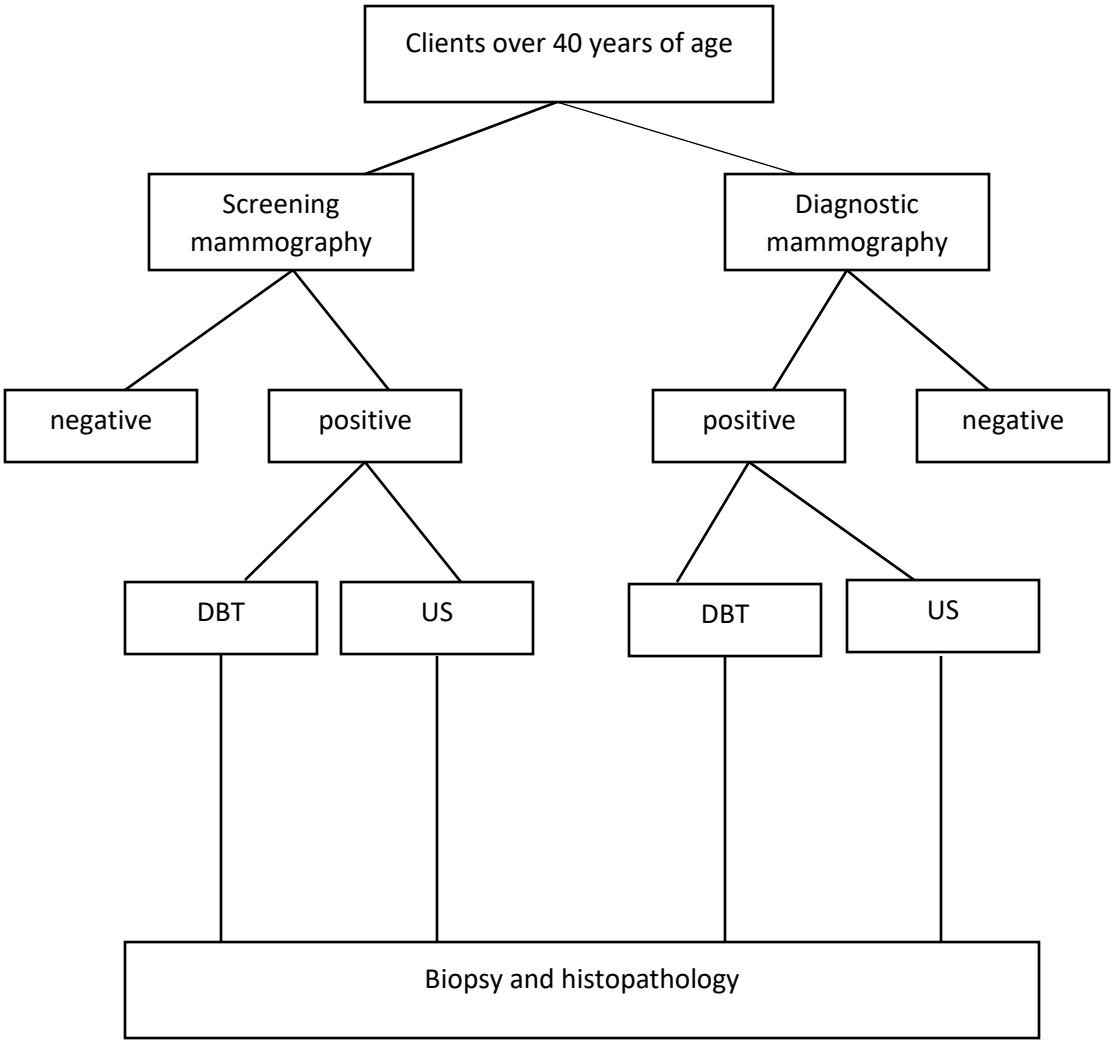


Figure 3. 63-year old female with a fibroadenoma measuring 1.3cm in the US.

A. Mediolateral oblique digital mammography. B. Mediolateral oblique DBT view. C. Breast US in transverse view. A well-circumscribed rounded hypodense mass is seen on DBT. On ultrasound, the mass appears to be hypoechoic with irregular margins. Readers 1 and 2 assessed this lesion as BI-RADS category 3 while reader 3 categorized the lesion as BI-RADS 2. On DBT. Reader 1 and 2 assessed the lesion as BI-RADS 4a, and reader 3 categorized it as BI-RADS 3 on breast ultrasound (retrieved from Kim et al., 2015).

2.7 Conceptual Framework

2.7.1 Schematic



2.8 Study Justification

Amongst the common occurring cancers in women, breast cancer is ranked at the top affecting 2.1 million women worldwide each year. It is considered the greatest cause of cancer-related deaths in women. Early detection is, therefore, an important entity in terms of treatment options, improved quality of life, and survival rates.

With the standard of practice, mammography has been long used for early detection of breast cancer but bears a limitation in that its sensitivity to dense breasts (a risk factor for breast cancer) is reduced therefore masking underlying pathology. Published studies have illustrated mitigation to this predicament by bringing in breast ultrasound and digital tomosynthesis as adjuncts to mammography and have shown great success. Both techniques were shown to immensely improve sensitivity and specificity to the detection of breast cancer however, the diagnostic accuracy of DBT compared to that of the US in characterizing breast lesions has not been well documented. No Kenyan studies have so far been done comparing the accuracy of the two modalities as adjuncts to 2D mammography and no data is available.

This study is aimed at filling this knowledge gap. From the results of this study, the radiology department may now be in a better position to determine which imaging strategy to adopt using local data thereby informing on the current practice. It will also serve as a baseline for further studies in this area with larger sample sizes and a longer study period

Digital breast tomosynthesis is currently a free service at KNH and is designated to be used as an adjunct to 2D mammography without additional costs to the clients.

The findings of the study informed the diagnostic accuracy of DBT compared to that of Breast US in the management practices of breast cancer patients at KNH.

2.9 Study Question

What is the diagnostic accuracy of DBT compared with that of breast US in the characterization of mammographic breast lesions?

2.10 Objectives

2.10.1 Broad Objective

To determine the diagnostic accuracy of DBT compared to that of the breast ultrasound in the characterization of mammographic breast lesions using histopathology as the gold standard.

2.10.2 Specific Objectives

1) To determine sociodemographic characteristics of clients undergoing mammography at KNH.
2) To characterize lesions seen on mammography with both DBT and Breast US using the BI-RADS categorization.
3) To determine the diagnostic accuracy of DBT using histopathology as the gold standard.
4) To determine the diagnostic accuracy of targeted breast US using histopathology as the gold standard.
5) To compare the diagnostic accuracy of DBT to that of breast US in the characterization of mammographic lesions using histopathology as the gold standard.

CHAPTER 3: METHODOLOGY

3.1 Study Design

A cross-sectional matched pairs design.

3.2 Study Site

The Kenyatta National Hospital is the largest referral facility in East and Central Africa. It is the teaching facility housing the University of Nairobi's School of Medicine. On an annual average, the department handles about 600 patients undergoing screening and diagnostic tests for breast cancer. In the year 2018, 608 patients underwent mammography. Out of these 147 required additional imaging for further characterization of the mammographic lesions. Fifty (50) patients had a DBT done and the remaining 97 had breast ultrasound done. The hospital has in place standard operating procedures that guide the screening and diagnosis of breast cancer.

3.3 Study Population

Kenyatta National Hospital being one of the National referral facilities handles mainly high-risk patients across various departments. More than half of the patients come in as referrals from surrounding health facilities. This study aimed to include all those patients who utilized the mammography and required additional imaging using both breast ultrasound and tomosynthesis to characterize their mammographic lesions.

3.4 Sample Size Calculation and Formula

3.4.1 Sample Size

Using the method given by Conner (35)

$$n = \frac{\left[SLF \times (\psi)^{1/2} + PF \times (\psi - \delta^2)^{1/2}\right]^2}{\delta^2}$$

Where,

ψ = Probability of disagreement between the techniques

$\delta = P_2 - P_1$, P_1 = sensitivity (specificity) of the reference technique, P_2 = sensitivity (specificity) of the alternative modality.

SLF = Significance level factor = 1.645, and PF = Power factor = 0.840 (See table below).

$$\psi = P_1 \times (1 - P_2) + (1 - P_1) \times P_2$$

Significance Level (%)	Significance Level Factor (SLF)	Power (%)	Power Factor (PF)
1	2.325	99	2.325
5	1.645	95	1.645
10	1.280	90	1.280
		80	0.840
		70	0.525

P_1 = Sensitivity of ultrasound gotten from a published study, set at 97% (35)

P_2 = Sensitivity of tomosynthesis set at 87% (to detect a difference of 10%)

$$\psi = 0.97 \times (1 - 0.87) + (1 - 0.97) \times 0.87 = 0.152$$

$$n = \frac{\left[1.645 \times (0.152)^{1/2} + 0.840 \times (0.152 - 0.01)^{1/2}\right]^2}{0.01^2} = 92$$

3.5 Sampling Procedure and Selection of Study Participants

The study participants were drawn from the patients who underwent mammography tests at the KNH radiology department. Patients who consented to be part of the study underwent tomosynthesis studies in the same room using the same machine. A breast ultrasound was done on the same patient in a different room by the principal investigator, who was blinded from the findings of the tomosynthesis and verified by the consultant radiologist. A purposive sampling procedure was used to identify patients to be included in the study until the sample size of 92 was arrived at. The same patients as sampled had both tests conducted, commencing with digital breast tomosynthesis and later followed by breast ultrasound.

3.6 Recruitment and Consenting Procedures

3.6.1 Inclusion Criteria

- ✓ clients aged 40 years and above

- ✓ Patients who presented for diagnostic mammography at KNH.
- ✓ Clients who presented for screening and found to have a mammographic lesion.
- ✓ Patients who had a biopsy taken and had a histopathological report.

3.6.2 Exclusion Criteria

- ✓ Gravid and breastfeeding patients.
- ✓ clients who were reluctant to give consent.
- ✓ Patients who had undergone neoadjuvant chemotherapy, radiotherapy, or had surgery on the same side of examination.
- ✓ Patients who had not had a biopsy taken or didn't have a histopathological report.

3.7 Equipment

The radiology department has a dedicated Digital mammography unit (GE Essential senographe) with DBT technology which serves all departments in the hospital.

Two high-resolution ultrasound machines (both with high-frequency transducers) were used in this study, one ultrasound machine was at the department of diagnostic imaging and radiation medicine UON and the other at the radiology department of KNH (GE Logiq S7 Expert and Toshiba Aplio 400 respectively). Both machines had linear probes allocated to breast imaging. These machines were operated by the radiology residents and validated by the consultant radiologists.

3.8 Study procedure

Study participants meeting the inclusion criteria were recruited into the study after giving informed consent. Digital breast tomosynthesis and digital mammography were performed by two trained and dedicated technologists to do 2D and DBT using the digital mammography unit. Breast compression was done as earlier described mediolateral oblique and single view DBT. A stack of 9 images was obtained at an angle of 15.6° between every two stacks. MLO digital mammography images and DBT MLO projection images were displayed on the computer screen for interpretation by the principal investigator and co-investigator (KNH consultant).

These images were assessed with particular focus paid to breast density pattern according to BI-RADS lexicon, presence of masses or lesions, lesion margins, presence of asymmetry,

assessment of architectural distortion if present, and assessment of calcifications if present. Any masses or lesions were described as seen on both DBT and digital mammography using the BIRADS system of classification of breast masses and their orientation in terms of spatial location noted. A breast ultrasound was done on the same patient in a different room by the PI then verified by a consultant radiologist (both the PI and the consultant radiologist will be blinded from the finding of the digital breast tomosynthesis).

Targeted breast ultrasound was performed with the patient in a supine position using a high-frequency linear transducer. Scanning protocol included gray-scale imaging of the mass lesions in the breast acquired in at least two planes – longitudinal and transverse. For each case, 2-4 B-mode US images of masses were saved for future reference.

The masses or lesions were characterized, as likely benign or malignant, and final assessment categories were assigned using the ACR BI-RADS ultrasound lexicon. BI-RADS final assessment for DBT and breast ultrasound was recorded. BI-RADS 2,3,4 and 5 lesions were biopsied and correlated with histopathological reports as the gold standard. The patients' demographic data such as age, sex, and menopausal status was entered in the data collection form by the principal investigator as per the attached data collection form in the appendices. This information was extracted from the existing pre-examination patient information form that was currently used for all patients seeking mammography at KNH.

3.9 Recruitment and Consenting Procedures

Once identified, the principal investigator or research assistant briefed the patients on the purpose and method of the study and attained verbal consent. After that, written approval was obtained on a pre-designed consent form (see appendix 1) that described the main goal of the study, the study procedure, and the potential risks and benefits of participating in the research. The consent form was also translated into Swahili for ease of understanding (appendix 2).

Any pertinent questions or concerns regarding the procedures were responded to at that point. This process was free from coercion and explicitly voluntary. Those who agreed to be participants were requested to offer a written informed consent form and countersigned by the investigator. Records were kept regarding reasons for non-participation of eligible participants, and a copy of the signed informed consent form was provided to the participant.

Study Variables

Variable	Description
Independent	Age, parity
Dependent	Breast Lesions
Intermediate	Breast Density

3.10 Data Collection and Management

Data were collected only after approval by the KNH-UoN ERC. This involved collection of patient biodata as per the attached data collection tool and analysis of the mammographic images. Mammographic findings for DM and DBT and US findings were recorded in the data collection tool and assigned a BIRADS score according to the BIRADS classification system. All data were stored in a password-protected computer and backup done on an external storage device e.g. compact Discs (CDs). Patients' mammographic images obtained during the study were stored in the GEPACS system according to the standard practice in force in the hospital as this formed part of patients' hospital records. There were no deviations from this practice.

3.10.1 Data Management and Analysis

The collected data were checked for completeness and accuracy before being entered into Microsoft Excel for analysis using STATA software version 15. The demographic characteristics were summarized and presented as medians with interquartile range, means with standard deviations, and as well as frequencies and proportions where applicable for continuous and categorical data. Analysis was performed on data obtained from matched image sets. The characterization of the lesions was analyzed using the BI-RADS system and presented as frequencies and proportions. The sensitivity and specificity of breast US and DBT were compared using the McNemar test. The diagnostic accuracy, specificity, positive predictive value, sensitivity, and negative predictive values (NPVs) of tests were computed as shown in Table 3 and used to determine the diagnostic precision of tomosynthesis and ultrasound in the detection of breast lesions. A p-value of 0.05 was taken as statistically significant.

3.10.2 Data collection procedures

A log was availed at the KNH radiology department for the principal investigator, research assistant, and enrolled patients. The data collected from eligible patients were entered and signed in the logbook. A structured survey questionnaire was used to gather all medical details from the participants. The Consultant and principal investigator reviewed all patients during admission

into the center. After that, the clients who fit the inclusion criteria and consent were recruited for the procedures. Upon undergoing the mammography, the eligible patients underwent tomosynthesis immediately post mammography in the same room before being taken to the sonography room for the ultrasound. Those participants who had undergone the procedures were interviewed to complete the questionnaire.

3.10.3 Data quality assessment

Quality assurance was enhanced throughout the study to ensure that the data collected were valid and reliable. The completeness of questionnaires was checked by the principal investigator at the end of each day during the collection of study data to ensure accuracy and completeness. The questionnaires were availed in English and Kiswahili and pre-testing of the study instrument was carried out in a non-study site to correct any bias, misinterpretation of the questions, and ambiguity. The validity of the study was ascertained by ensuring that all instruments used for data collection reflected the objectives of the study. The research instrument was validated by the University of Nairobi supervisors.

3.11 Study Closure and Dissemination of Results

All participants were issued a report of the findings. A report of the study findings was presented to the Department of Radiology KNH, University of Nairobi, and copies also sent to the KNH-UoN ERC. A manuscript of this entire dissertation will be drafted and submitted to various journals for publication.

3.12 Study Limitations

Interobserver variability introducing observer bias while conducting either ultrasonography or tomosynthesis. To mitigate this, the same consultant radiologist was engaged throughout the study and used the same tomosynthesis and ultrasound machines with the same resolution and frequency; SOPs for performing the procedures were also followed to the latter.

Equipment breakdown, and lack of funds from the patients. The ongoing coronavirus pandemic led to the reduction of the number of clients presenting in the mammography unit. Shortage of personal protective equipment (PPE) also was a predicament in the ongoing pandemic.

3.13 Ethical consideration

This study protocol and the template for the informed consent form found in Appendix 1 and any subsequent modifications to this form were submitted for review and approval by the Kenyatta National Hospital/University of Nairobi Ethics Research Committee (KNH-UoN ERC) before the initiation of the study. The study was conducted as per the scientific content and compliance with applicable research and human subjects regulations.

Low-dose mammography protocols were used following the ``As Low As Reasonably Achievable (ALARA)" principle. The addition of DBT to digital mammography led to a slight increase in radiation dose by approximately double the dose of the standard two-view digital mammography for each breast imaged. This increase in dose was still lower than the maximum acceptable dose in mammography (3mGy per breast).

All the study participants were subjected to an opt-out consenting procedure and were only enrolled upon voluntarily signing the consent form. No pain management medications were provided during the study. For patients who required biopsy for correlation, the biopsy process was expedited by processing the request form immediately for the biopsy to be carried out without delay. The principal investigator liaised with the pathology lab to ensure the timely release of the reports. Once the histopathology results were out, the referring physician was informed to ensure timely care. The participant's details were de-identified by the use of assigned unique identifiers, only applicable to the study. This coded information was uploaded to the excel sheet and was password protected. Back-up data was kept in a password-encrypted external hard drive, only known to the PI.

CHAPTER 4: RESULTS

4.1 Patients demographic characteristics

Participants were enrolled in the study from December 2020 to May 2021 with a sample size of 92. All the 92 participants were female. The majority were between 50-59 years (39.1%) followed by 40-49 (27.2). Only 12% were aged 70 years and above. The mean age of the participants was 56.4 (SD 10.2) years. The median age was 56 (IQR 48.5 – 63.5) years, with an age range from 40 to 92 years. The highest level of education was primary education (43.5%). Regarding the menopausal status, 72.8% were postmenopausal. Usage of hormonal contraceptives and parity of 3 and below was at 62.0%. only 16.3% of the respondents had a family history of breast cancer (Table 1).

Table 1. Demographic and clinical characteristics of the study participants

	Frequency (*n=92*)	**Percent (%)**
Age		
40-49	25	27.2
50-59	36	39.1
60-69	20	21.7
70+	11	12.0
Education (highest level)		
Primary	40	43.5
Secondary	26	28.3
Tertiary	14	15.2
None	12	13.0
Menopausal status		
Premenopausal	16	17.4
During	9	9.8
Postmenopausal	67	72.8
Hormonal contraceptive		
Yes	57	62.0
No	35	38.0
Parity		

0-3	57	62.0
4-6	30	32.6
7+	5	5.4
Family history of breast cancer		
Yes	15	16.3
No	77	83.7

4.2 Reason for mammography and clinical indication

The majority of the mammograms performed were diagnostic mammograms (82.1%, 82/92) only 10 women presented with screening mammography during the study period. Among the symptomatic women 62 (75.6%) presented with breast lumps and only 1 (1.2%) with peau d'orange.

Table 2. Mammography type and clinical indication

	Frequency (*n=92*)	**Percent (%)**
Reason for mammography		
Screening	10	10.9
Diagnostic	82	89.1
If diagnostic	**Frequency (*n/82*)**	**Percent (%)**
Lump	62	75.6
Pain	29	35.4
Nipple discharge	1	1.2
Nipple retraction	5	6.1
Peaud'orange	3	3.7

4.3 Breast density

On Mammographic breast density assessment, most clients had heterogeneously dense breasts (ACR C) at 48.9%, with the least common type being predominantly fatty (ACR A). extremely dense breasts (ACR D) were at 7.6% (Table 3).

Table 3. Digital Mammography

	Frequency (*n=92*)	**Percent (%)**
Breast density		
ACR A	9	9.8
ACR B	31	33.7
ACR C	45	48.9
ACR D	7	7.6

4.4 DBT lesion characteristics and final BI-RADS score

BI-RADS lesion descriptors on DBT using mammography lexicon (mass shape, margins, density, architectural distortion, and micro-calcifications) are summarised in Table 4.

The Chi-square test for homogeneity was used to assess if the distribution of the benign and malignant were the same for the different lesion characteristics. The results indicate that the distribution of benign is statistically different from those of malignant for all lesion characteristics except for Microcalcifications.

According to the mammographic BI-RADS descriptors assessment used for DBT, most of the breast lesions were categorized as BI-RADS 4C (34.8%), followed by BI-RADS 5 (31.5%), then BI-RADS 3 (13.0%) and BI-RADS 4B (12.0%). The 2 least categories were BI-RADS 2 (7.6%) and BI-RADS 4A (1.1).

Table 4. DBT Lesion Characteristics and BI-RADS score

Lesion characteristics on DBT	Benign	Malignant	p-value
Shape			**<0.001**
Irregular	2	39	
Oval	8	3	
Round	9	31	
Margin			**<0.001**
Circumscribed	17	8	
Indistinct	1	10	
Microlobulated	0	19	
Obscured	1	8	
Spiculated	0	28	
Density			**<0.001**
Equal	16	21	
High	3	52	
Microcalcifications			**<0.010**
No	18	47	
Yes	1	26	
Architectural distortion			**<0.006**
No	18	45	
Yes	1	28	

BIRADS Category	Frequency *(n=92)*	Percentage (%)
2	7	7.6
3	12	13.0
4A	1	1.1
4B	11	12.0
4C	32	34.8
5	29	31.5

4.5 Breast US lesion characteristics and final BI-RADS score

Breast US descriptors (mass shape, orientation, lesion boundary, posterior features, and echo pattern) are summarised in table 5.

The results indicate that the distribution of benign is statistically different from those of malignant for all lesion characteristics except for Echogenicity and Microcalcifications. On breast US descriptors, the majority of breast lesions were also classified as BI-RADS 4C (34.8%). The least common scores were BI-RADS 3 and 4A scoring (6.5% and 4.3% respectively).

Table 5. US Lesion Characteristics and BI-RADS score

Lesion characteristics on the US	**Benign**	**Malignant**	**p-value**
Shape			**<0.001**
Irregular	3	51	
Oval	13	4	
Round	3	18	
Margin			**<0.001**
Angular	2	23	
Circumscribed	15	4	
Indistinct	2	14	
Microlobulated	0	16	
Spiculated	0	16	
Echogenicity			**0.466**
Hypoechoic	19	71	
Non-hypoechoic	0	2	
Orientation			**<0.001**
Not parallel	5	70	
Parallel	14	3	
Lesion boundary			**<0.001**
Abrupt interface	16	10	
Echoic halo	3	63	

Posterior feature			**<0.001**
Combined	1	28	
Enhancement	11	3	
No featured	6	4	
Shadowing	1	38	
Microcalcifications			**0.448**
No	18	62	
Yes	1	11	

BIRADS category	**Frequency (*n=92*)**	**Percent (%)**
2	10	10.9
3	6	6.5
4A	4	4.3
4B	10	10.9
4C	32	34.8
5	30	32.6

4.6 Histopathology results

Of the 92 women, 73 (79.3%) had malignant lesions with the rest being benign 19 (20.7%), a statistically significant difference in their proportions, ***p<0.001***. The commonest malignancy was invasive ductal carcinoma found in 70 (76.1%) women. On the other hand, the most common benign lesion was fibroadenoma ascertained in 14 (15.2%) patients.

Table 6. Histopathology Results

	Frequency (*n=92*)	**Percent (%)**
Result		
Benign	19	20.7
Malignant	73	79.3
Diagnosis		
Epidermoid cyst	1	1.1
Fibroadenoma	14	15.2
Fibrocystic change	4	4.3

Invasive ductal carcinoma	70	76.1
Metastatic carcinoma	1	1.1
Mucinous breast carcinoma	1	1.1
Papillary DCIS	1	1.1

4.7 Diagnostic accuracy of DBT

The sensitivity and specificity of the DBT were 95.8% and 80.0% respectively when compared to the Histopathology, with a Positive Predictive value of 94.5% and a Negative Predictive Value of 84.2%. The diagnostic accuracy was 92.4%.

Table 8: DBT and Histopathology

	Histopathology		
DBT	Positive	Negative	**Total**
Positive	69	4	**73**
Negative	3	16	**19**
Total	**72**	**20**	**92**

4.8 Diagnostic accuracy of breast US

The sensitivity and specificity of the breast ultrasound were 98.6% and 78.9% when compared to the Histopathology, with a Positive Predictive value of 94.7% and a Negative Predictive Value of 93.8%. The diagnostic accuracy was 94.6%

Table 7. Breast Ultrasound and Histopathology

	Histopathology		
Breast Ultrasound	Positive	Negative	**Total**
Positive	72	4	**76**
Negative	1	15	**16**
Total	**73**	**19**	**92**

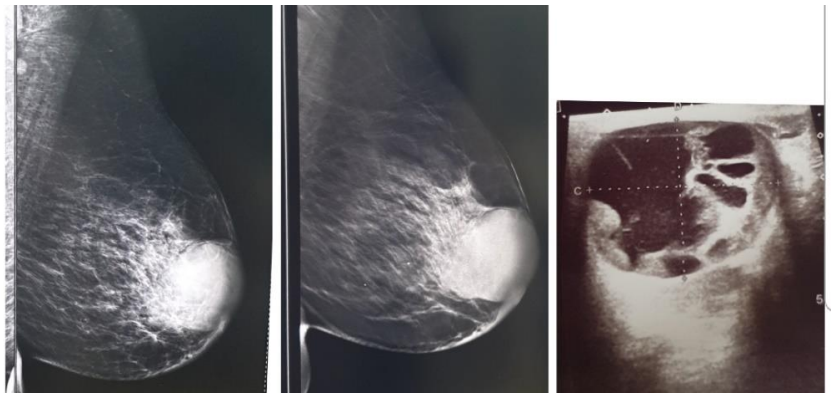
4.9 Diagnostic accuracy of DBT compared to that of breast US in the characterization of mammographic lesions

The sensitivity and specificity of DBT and Breast were not statistically significant as shown in table 8.

Table 8. Diagnostic accuracy of DBT vs Breast US

Diagnostic index	DBT	Breast US	p-value
Sensitivity	95.8%	98.6%	0.251
Specificity	80.0%	78.9%	0.854

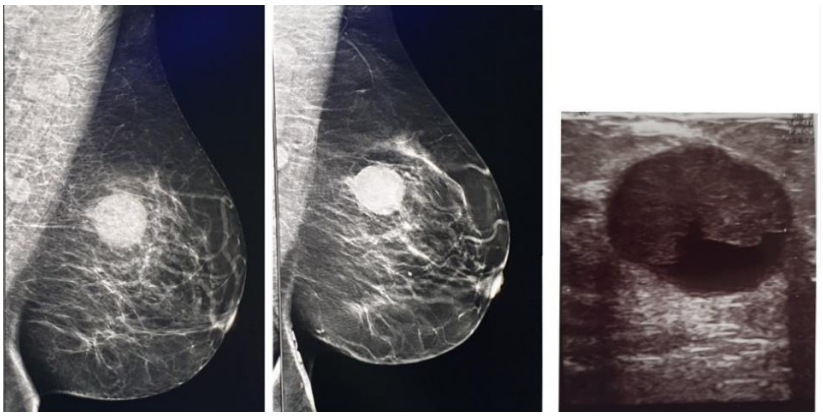
4.10 Imaging description of reference cases



A **B** **C**

Figure 4. A 73-year-old woman with mucinous (colloid) breast carcinoma showing,

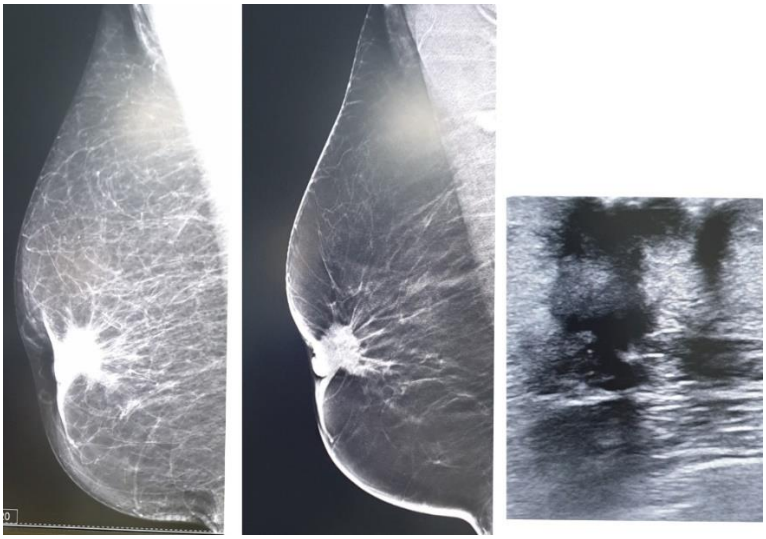
A: Mediolateral oblique digital mammography view. **B**. Mediolateral oblique DBT (1-mm section) view. **C.** Transverse ultrasound view. Round high density, partially circumscribed retro areolar mass observed on DBT. On breast ultrasound, a complex cystic mass with solid components is seen. It shows both posterior enhancement and shadowing. The mass was categorized as BI-RADS 4C on DBT and BI-RADS 5 on ultrasound.



A **B** **C**

Figure 5. A 57-year-old woman with Papillary DCIS showing,

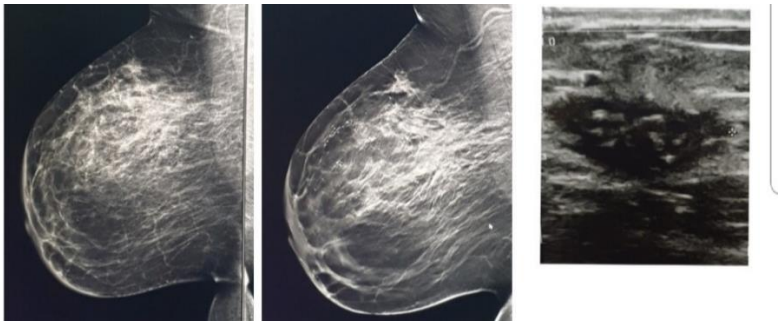
A: Mediolateral oblique digital mammography view**. B**. DBT image in mediolateral oblique view**. C.** breast ultrasound in transverse view. A round high-density mass, partially circumscribed (obscured posteriorly with comet tails) is seen on DBT. On ultrasound, a complex cystic and solid breast mass is seen. It is rounded, well-circumscribed, and shows both shadowing and posterior enhancement. This mass was graded BI-RADS 4C on DBT and 5 on ultrasound.



A **B** **C**

Figure 6. 63-year old woman with invasive ductal carcinoma showing,

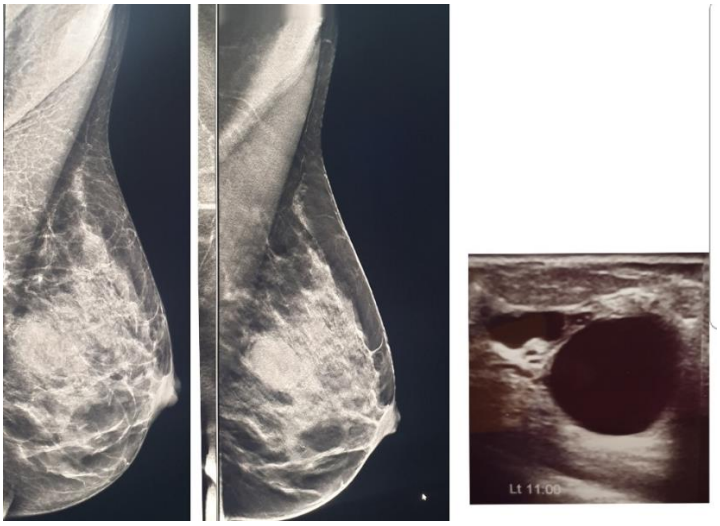
A: Mediolateral oblique digital mammography view. **B.** Digital breast tomosynthesis in mediolateral oblique view**. C.** Breast ultrasound (US) in transverse view. A high density spiculated retro areolar mass seen on DBT. The mass is associated with nipple retraction. On ultrasound, the mass is hypoechoic, irregular in shape with micro lobulated margins, and demonstrates posterior acoustic shadowing. The lesion was categorized as BI-RADS 5 on both DBT and breast US.



A **B** **C**

Figure 7. 66-year old with invasive ductal carcinoma showing,

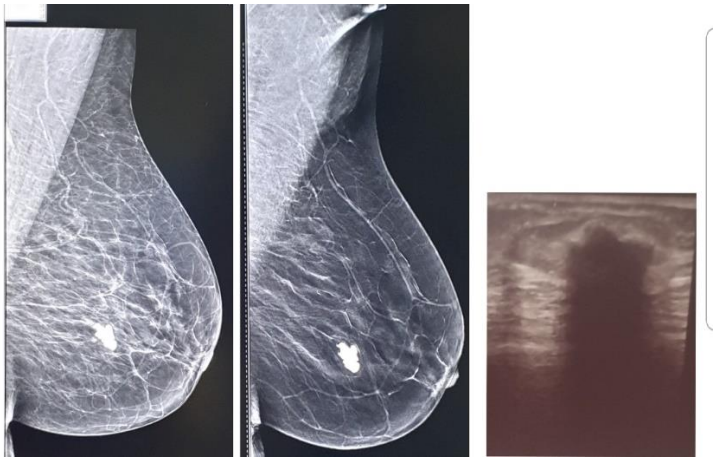
A: Mediolateral oblique digital mammography view. **B**. Mediolateral oblique DBT view. **C.** Breast ultrasound in transverse view. A spiculated high-density mass associated with segmental pleomorphic microcalcification is seen on DBT. On ultrasound, the mass is spiculated, hypodense with areas of multiple punctate microcalcifications. The mass was categorized as BI-RADS 5 on both DBT and US.



A **B** **C**

Figure 8. 55-year old with fibrocystic change showing,

A: Mediolateral oblique digital mammography view. **B.** Mediolateral oblique digital breast tomosynthesis view. **C**. Transverse US view. An oval circumscribed medium density mass with an adjacent smaller oval-shaped mass seen on DBT. There are associated pleomorphic segmental microcalcifications seen on DBT. On ultrasound, there is a well-circumscribed, anechoic, round, thin-walled cyst with an associated ductal dilatation. The mass was scored BI-RADS 4A on the US and BI-RADS 4A on ultrasound.



A **B** **C**

Figure 9. 51-year old woman with fibroadenoma showing,

A: Mediolateral oblique digital mammography view. **B.** Digital breast tomosynthesis in mediolateral oblique view. **C**. Breast ultrasound in transverse view. Coarse popcorn calcification seen on DBT, on ultrasound, there is an oval mass wider than tall with a central area of shadowing. This mass was scored BI-RADS 2 on both DBT and ultrasound

CHAPTER 5: DISCUSSION, CONCLUSION, AND RECOMMENDATION

5.1 DISCUSSION

The main objective of this study was to compare the diagnostic accuracy of DBT and targeted breast US in the characterization of mammographic lesions. The results indicate that the diagnostic accuracy of both modalities was similar in characterizing lesions seen on mammography.

5.1.1 Sociodemographic characteristics

In the study, the majority of women had attained primary education as the highest level of education.

Sayed et al, in 2017 in a study on ethnicity and breast cancer characteristics in Kenya ascertained that most of the participants received only primary education or no form of education at all (36).

Similarly Gueye et al, in Dakar 2017, conducted a study to investigate the relationship between sociodemographic factors and delays in presentation with breast anomalies and found that 46.3% of the patients were illiterate (37).

On the contrary, Opili et al, in 2019 investigated the risk factors associated with breast cancer among women in Tranz-Nzoia Kenya. It was ascertained that the majority of the participants had attained university education (considered the highest level) because they were mostly from the urban setting and were government employees. However, the study concluded that there was no statistical significance between the risk of breast cancer and level of education (38).

In our study, most women were aged between 50 to 59 years (39.1%). Of all these 92 women, 67 (72.8%) were post-menopausal. This is in contrast with a study done by Opili et al, in Tranz-Nzoia 2019 which revealed that most of the participants aged between 41-50 years (premenopausal) and age had a statistically significant relationship to the risk of breast cancer. The study implied that the risk of breast cancer increased with increasing age. The older one became, the higher the chances of suffering from breast cancer due to the abnormal changes that occurred in the breast through the aging process that are due to the hormonal changes such as the decreasing levels of estrogen (38). Similarly, a study conducted by Gueye et al, in Dakar 2017, found that 65% of the women were premenopausal at the time of diagnosis (37).

In our study, 62% of the women had a history of use of hormonal contraceptives which included combined oral contraceptives, implants, and injectables.

The risk of breast cancer is higher among women who use or have recently used hormonal contraceptives (20 % risk) than among women who have never used hormonal contraceptives, and this risk is also increased with longer durations of use albeit the absolute risk is small (39).

Rispah T et al, in 2016 conducted a study on aggressive breast cancer in western Kenya. It was found that more than half of the patients used either injectable or pill contraceptives (40).

In our study, 16.3% of the participants had a positive family history of breast cancer. This compares favorably with a study from Dakar by Gueye et al, where 13.5% of the participants had a family history of breast cancer. In contrast, a study conducted by Sayed et al, coordinated by the Aga Khan Hospital Nairobi Kenya with 823 female participants, among 11 hospitals in 2017, illustrated that most of the patients had no history of breast cancer (36).

5.1.2 Mammographic lesion characterization on DBT

Our study shows out of the 73 malignant masses on DBT+FFDM, 53.4% were irregular-shaped, with spiculated margins (38.4%) and of high density (71.2%) whereas, 89.4 % benign lesions were well circumscribed and 84.2% of equal density. This compares well with a study conducted by Sanmugasiva V et al, in 2020 who found that in a sample of 258 masses, 144 were malignant with 90.9% of these having irregular shape, 96.7% spiculated margins, and 87.1% being of high density. Furthermore, 90.2% of benign lesions were well-circumscribed and 77.8% had equal density (41).

5.1.3 Mammographic lesion characterization on breast ultrasound

This study has shown that 69.9% of the malignant masses were irregularly shaped, with similar frequencies for both spiculated and microlobulated margins (84.2%), and anti-parallel (95.9%). The benign lesions were mostly well-circumscribed (78.9%), oval (68.4%), and parallel in orientation (73.6%). This compares well to a study by Priyanka et al 2019 which characterized malignant masses as irregular shaped (90%), spiculated (45%), and 75% anti-parallel. On the other hand, benign masses were predominantly well-circumscribed (94.7%). Sonomammograhic characterization emphasizes the ability to differentiate benign from malignant lesions.

5.1.4 Diagnostic accuracy of DBT using histopathology as the gold standard

This study has shown that the sensitivity and specificity of DBT were 95.8% and 80.0% when compared to histopathology. The positive predictive value was 94.5% and the negative predictive value was 84.2% with a diagnostic accuracy of 92.4%

In this study, there were fewer benign cases (20.7%) compared to malignant cases (79.3%), with many patients presenting with abnormal mammograms. This may be because most of the patients coming to Kenyatta as referrals from other facilities were presenting late with advanced breast disease. Increasing age was also seen to be a key factor for this especially the postmenopausal women. In a local study done at the Kenyatta National Hospital by Otieno et al, in 2010 for 166 patients, three reasons contributed to the delayed presentation of patients receiving treatment for breast cancer. The first was reassurance from the primary health professional that they had a benign condition and shouldn't worry without any biopsy (in 24.1% of the patients). The second reason was painless symptomatology (23.5% of the patients), and the third was fear of being told they have breast cancer (19.9% of the patients) (42).

In the recent studies carried out in the regional and developed countries, DBT has proved to markedly improve the sensitivity and specificity in the detection and characterization of mammographic lesions.

Sahar M et al, in 2014 Egypt compared the accuracy of DBT and digital mammography in the evaluation of different breast lesions (using histology as gold standard) and found that the sensitivity, specificity, and accuracy of digital mammography when combined with DBT improved to 94.5%, 74%, and 89.7% from 60%, 20.7% and 48% with digital mammography alone (43).

In 2016, Mariscotti et al in a retrospective multi-reader study investigated the interpretive performance of DBT as an adjunct to 2D mammography versus 2D mammography alone to detect and characterize invasive lobular carcinoma. It was confirmed that when digital mammography was combined with DBT, the sensitivity markedly improved (85% sensitivity) compared to DM alone (70% sensitivity) (27).

Gilbert et al, in a retrospective study in 2015, on the accuracy of DBT for depicting subgroups of breast cancer in the United Kingdom, concluded that for those patients with dense breasts, the

sensitivity of digital breast tomosynthesis as an adjunct to mammography was 93% while the specificity was at 70% (44).

5.1.5 Diagnostic accuracy of breast US using histopathology as the gold standard

This study has shown that the sensitivity and specificity of the breast ultrasound was 98.6% and 78.9% respectively when compared to the histopathology, with a Positive Predictive value of 94.7% and a Negative Predictive Value of 93.8%. The diagnostic accuracy was 94.6%. This is in contrast with a study by Mohamed R et al, in Egypt (2019) which, investigated the role of breast ultrasound as an adjunct to mammography in 100 patients with mammographic dense breasts and found that breast ultrasound as an adjunct to mammography had a sensitivity 100%, specificity of 93% with positive and negative predictive values at 91% and 100% respectively still using histopathology as the gold standard (30). This study evaluated breast lesions using FFDM and the breast US independently and in combination in women with dense breasts.

5.1.6 Diagnostic accuracy of DBT compared to that of breast US to characterize mammographic lesions

Published studies comparing the diagnostic accuracy of digital breast tomosynthesis to that of breast ultrasound in the characterization of lesions seen on mammography are limited. In this study, the sensitivity of DBT and breast US (95.8% vs. 98.6%, p=0.251) and specificity (80.0% vs 78.9%, p=0.854) were not statistically significant. This shows that the diagnostic accuracy of DBT and breast US were quite similar in the characterization of mammographic lesions.

Kim et al, in 2015 carried out a retrospective multi-reader study comparing the diagnostic accuracy of DBT versus breast ultrasound to characterize and distinguish benign from malignant lesions visualized on digital mammography (DM) in 119 women with breast lesions. DBT had a sensitivity of 97.3% and a specificity of 44% while breast US had a sensitivity of 98.7% and a specificity of 39.4% and concluded that the diagnostic accuracy of DBT was similar to that of breast US in characterizing lesions already seen on mammography (9). The low specificity was attributed to having a study population that was cancer-enriched and composed of mammographically abnormal findings. Moreover, the readers tended to assess lesions more suspiciously than in a routine clinical setting (9).

Ganime et al, in 2017, conducted a study to compare the diagnostic performance and screening recall rates of digital breast tomosynthesis and ultrasound added to conventional mammography in BI-RADS category 0 and revealed the DBT had a sensitivity of 97% and a specificity of 82% while breast ultrasound having a 93% sensitivity and a specificity of 79%. The study concluded that DBT reduced recall rates and showed better diagnostic performance than breast US for BI-RADS category 0 (12). However, no p-values were indicated in this study.

5.2 Conclusion

This study has shown that the diagnostic accuracy of DBT compared to that of targeted breast ultrasound in the characterizing breast lesions depicted on mammography was similar. The diagnostic accuracy of both digital breast tomosynthesis and breast ultrasound were high (92.4% and 94.6% respectively) with p-values of 0.251 for sensitivity and 0.854 for specificity (not statistically significant) and patients can benefit from either modality.

The main limitation of DBT was that it could not distinguish whether a circumscribed lesion is solid, cystic, or a complex cyst but ultrasound could differentiate the two.

5.3 Limitations

- The sample size was small thereby restricting the generalization of results to a larger target group.

5.4 Recommendations

- Increase clinician awareness of the available existing and new breast imaging modalities is crucial.
- There is a need to sensitize policymakers for screening mammography in our population
- Repackaging of breast imaging protocols where correlative ultrasound or DBT is done for patients with BI-RADS category 0 on the same day as the mammogram. This would be beneficial to patients so that, inconclusive findings on mammography can be correlated at the same sitting and save the patients additional cost and time.
- A randomized controlled study (RCT) to be done in the future purposefully to compare the diagnostic accuracy of DBT to that of the breast US with a control group for statistical reliability thus enable changes in protocols.

- Studies replicating this study with a larger sample size and a longer study period preferably at multiple sites.
- Filing of histopathology reports in the interventional radiology department for quick identification of discordant results that may need a repeat biopsy.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov 1;68(6):394–424.

2. Adeloye D, Sowunmi OY, Jacobs W, David RA, Adeosun AA, Amuta AO, et al. Estimating the incidence of breast cancer in Africa: a systematic review and meta-analysis. J Glob Health [Internet]. 2018 Jun [cited 2019 Sep 3];8(1):010419. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29740502

3. Azubuike SO, Muirhead C, Hayes L, McNally R. Rising global burden of breast cancer: The case of sub-Saharan Africa (with emphasis on Nigeria) and implications for regional development: A review. World J Surg Oncol. 2018;16(1):1–13.

4. Wengert GJ, Helbich TH, Kapetas P, Baltzer PA, Pinker K. Density and tailored breast cancer screening: practice and prediction – an overview. Acta Radiol Open. 2018;7(9).

5. Thigpen D, Kappler A, Brem R. The Role of Ultrasound in Screening Dense Breasts—A Review of the Literature and Practical Solutions for Implementation. Diagnostics [Internet]. 2018 Mar 16 [cited 2019 Sep 11];8(1):20. Available from: http://www.mdpi.com/2075-4418/8/1/20

6. Hooley RJ, Durand MA, Philpotts LE. Advances in Digital Breast. Am J Roentgenol. 2017 Feb 27;208Tomosyn(2):256–66.

7. Exhibit E, Pereira AC. Recent advances in breast imaging. 2013;

8. Paper O. Comparison of Digital Breast Tomosynthesis and Digital Mammography for Detection of Breast Cancer in Kuwaiti Women. 2019;90805:10–5.

9. Kim SA, Chang JM, Cho N, Yi A, Moon WK. Characterization of breast lesions: comparison of digital breast tomosynthesis and ultrasonography. Korean J Radiol. 2015;16(2):229–38.

10. Wang L. Early Diagnosis of Breast Cancer. Sensors (Basel). 2017 Jul 5;17(7).

11. Evans A, Trimboli RM, Athanasiou A, Balleyguier C, Baltzer PA, Bick U, et al. Breast ultrasound : recommendations for information to women and referring physicians by the European Society of Breast Imaging. 2018;449–61.

12. Emlik GD, Poyraz N, Altunkeser A. Digital breast tomosynthesis and ultrasonography: Diagnostic performance and effect on recall rates versus digital mammography in category 0. Int J Clin Exp Med. 2017;10(7):10668–75.

13. Seely JM, Alhassan T. Screening for breast cancer in 2018-what should we be doing

today? Curr Oncol. 2018;25(Suppl 1):S115–24.

14. Freer PE. Mammographic Breast Density: Impact on Breast Cancer Risk and Implications for Screening. RadioGraphics. 2015 Mar;35(2):302–15.

15. Karimi SE, Rafiey H, Sajjadi H, Nosrati Nejad F. Identifying the Social Determinants of Breast Health Behavior: a Qualitative Content Analysis. Asian Pac J Cancer Prev. 2018 Jul 27;19(7):1867–77.

16. Patel K, Kanu M, Liu J, Bond B, Brown E, Williams E, et al. Factors influencing breast cancer screening in low-income African Americans in Tennessee. J Community Health [Internet]. 2014 Oct [cited 2019 Sep 28];39(5):943–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24554393

17. Antabe R, Kansanga M, Sano Y, Kyeremeh E, Galaa Y. Utilization of breast cancer screening in Kenya : what are the determinants ? 2020;2:1–9.

18. Monticciolo DL, Newell MS, Moy L, Niell B, Monsees B, Sickles EA. Breast Cancer Screening in Women at Higher-Than-Average Risk: Recommendations From the ACR. J Am Coll Radiol [Internet]. 2018;15(3):408–14. Available from: https://doi.org/10.1016/j.jacr.2017.11.034

19. Nazari SS, Mukherjee P. An overview of mammographic density and its association with breast cancer. Vol. 25, Breast Cancer. Springer Tokyo; 2018. p. 259–67.

20. Freer PE. Mammographic Breast Density: Impact on Breast Cancer Risk and Implications for Screening. RadioGraphics [Internet]. 2015 Mar 12 [cited 2019 Oct 1];35(2):302–15. Available from: http://pubs.rsna.org/doi/10.1148/rg.352140106

21. Yang L, Zhou C. Comparison of ultrasound and digital mammography plus tomosynthesis in determining benign and malignant breast lesions using pathology as a gold standard, in 102 Chinese women. Hell J Nucl Med. 2019;22(1):36–42.

22. Sree SV, Ng EY-K, Acharya RU, Faust O. Breast imaging: A survey. World J Clin Oncol. 2011 Apr 10;2(4):171–8.

23. Prasad SN, Houserkova D. The role of various modalities in breast imaging. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2007;151(2):209–18.

24. Sree SV, Ng EYK, Acharya U R, Tan W. Breast imaging systems: A review and comparative study. J Mech Med Biol. 2010;10(1):5–34.

25. El Bakry RAR. Breast tomosynthesis: A diagnostic addition to screening digital mammography. Egypt J Radiol Nucl Med. 2018;49(2):529–35.

26. Nakashima K, Uematsu T, Itoh T, Takahashi K, Nishimura S, Hayashi T, et al.

Comparison of visibility of circumscribed masses on Digital Breast Tomosynthesis (DBT) and 2D mammography: are circumscribed masses better visualized and assured of being benign on DBT? Eur Radiol [Internet]. 2017;27(2):570–7. Available from: http://dx.doi.org/10.1007/s00330-016-4420-5

27. Mariscotti G, Durando M, Houssami N, Zuiani C, Martincich L. Digital breast tomosynthesis as an adjunct to digital mammography for detecting and characterising invasive lobular cancers : a multi-reader study. Clin Radiol [Internet]. 2016; Available from: http://dx.doi.org/10.1016/j.crad.2016.04.004

28. Rapelyea JA, Marks CG. Breast Ultrasound Past, Present, and Future. Breast Imaging. 2018;

29. Hooley RJ, Scoutt LM, Philpotts LE. Breast ultrasonography: State of the art. Radiology. 2013;268(3):642–59.

30. El MR, Mousa WA, Mishmisha NR. Role of sonography as an adjunct to mammography in women with dense breasts. :876–80.

31. Lee WK, Chung J, Cha E, Lee JE, Kim JH. Digital breast tomosynthesis and breast ultrasound : Additional roles in dense breasts with category 0 at conventional digital mammography. 2016;85:291–6.

32. Mokhtar O, Abd S, Gamal G, Naguib E, Gomaa M. 3D digital breast tomosynthesis versus US in evaluating breast asymmetries. 2020;0.

33. Rao AA, Feneis J, Lalonde C. A Pictorial Review of Changes in the BI-RADS Fifth Edition 1. 2016;

34. Berment H, Becette V, Mohallem M, Ferreira F, Chérel P. Masses in mammography: What are the underlying anatomopathological lesions? Diagn Interv Imaging. 2014;95(2):124–33.

35. Connor RJ. Sample Size for Testing Differences in Proportions for the Paired-Sample Design. 2014;43(1):207–11.

36. Sayed S, Moloo Z, Wasike R, Bird P, Oigara R, Wambui F, et al. Ethnicity and breast cancer characteristics in Kenya. Breast Cancer Res Treat. 2017;

37. Gueye M, Modou S, Gueye K, Diallo M, Thiam O, Mbodji A, et al. Sociodemographic Factors Associated with Delays in Breast Cancer. 2017;455–63.

38. RISK FACTORS ASSOCIATED WITH BREAST CANCER AMONG WOMEN IN TRANS-NZOIA COUNTY , KENYA , MASTER OF SCIENCE (Epidemiology) JOMO KENYATTA UNIVERSITY OF. 2019;

39. Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø. Contemporary Hormonal Contraception and the Risk of Breast Cancer. N Engl J Med. 2017;377(23):2228–39.

40. Sawe RT, Kerper M, Badve S, Li J, Sandoval-Cooper M, Xie J, et al. Aggressive breast cancer in western Kenya has early onset, high proliferation, and immune cell infiltration. BMC Cancer [Internet]. 2016;16(1):1–15. Available from: http://dx.doi.org/10.1186/s12885-016-2204-6

41. Sanmugasiva VV, Ramli Hamid MT, Fadzli F, Rozalli FI, Yeong CH, Ab Mumin N, et al. Diagnostic accuracy of digital breast tomosynthesis in combination with 2D mammography for the characterisation of mammographic abnormalities. Sci Rep. 2020;10(1):1–11.

42. Otieno ES, Micheni JN, Kimende SK, Mutai KK. Delayed presentation of breast cancer patients. 2010;87(4):147–50.

43. Mansour S, Adel L, Omar OS. Comparative study between breast tomosynthesis and classic digital mammography in the evaluation of different breast lesions. Egypt J Radiol Nucl Med [Internet]. 2014;45(3):1053–61. Available from: http://dx.doi.org/10.1016/j.ejrnm.2014.03.007

44. Gilbert FJ, Tucker L, Gillan MGC, Willsher P, Cooke J, Duncan KA, et al. Accuracy of digital breast tomosynthesis for depicting breast cancer subgroups in a UK retrospective reading study (tommy trial)1. Radiology. 2015;277(3):697–706.

APPENDICES

Appendix 1: Information and Consent Form (English)

STUDY TITLE: A Comparison Between Digital Breast Tomosynthesis And Ultrasound in The Characterization of Mammographic Breast Lesions Using Histopathology as The Gold Standard at Kenyatta National Hospital: A cross-sectional matched pairs design.

Kenyatta National Hospital, Nairobi, Kenya

Principal Investigator: Dr. Naaila B. Kuppuswamy (Mmed student, University of Nairobi)

Co-Investigators: Dr Gladys Mwango (University of Nairobi), Dr Beatrice Mugi **(**Kenyatta National Hospital).

Introduction:

I would like to tell you about a study being conducted by the above-listed researchers. The purpose of this consent form is to give you the information you will need to help you decide whether or not to be a participant in the study. Feel free to ask any questions about the purpose of the research, what happens if you participate in the study, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide to be in the study or not. This process is called 'informed consent.' Once you understand and agree to be in the study, I will request you to sign your name on this form. You should understand the general principles which apply to all participants in a medical research: i) Your decision to participate is entirely voluntary ii) You may withdraw from the study at any time without necessarily giving a reason for your withdrawal iii) Refusal to participate in the research will not affect the services you are entitled to in this health facility or other facilities. We will give you a copy of this form for your records.

May I continue? YES / NO

WHAT IS THIS STUDY ABOUT?

The researchers listed above are conducting a research on the diagnostic performance of digital breast tomosynthesis compared to that of breast ultrasound to characterize mammographic lesions and use histopathology as the gold standard for confirmation. The findings of the study

will inform the diagnostic accuracy of DBT compared to that of breast US in the management practices of breast cancer patients at KNH. Approximately 92 patients will be selected for this study. We are asking for your consent to consider participating in this study.

WHAT WILL HAPPEN IF YOU DECIDE TO BE IN THIS RESEARCH STUDY?

If you agree to participate in this study, the following things will happen:

- You will undergo both digital breast tomosynthesis and breast ultrasound to characterize the lesion seen on mammography using BI-RADS reporting system.
- Your final BI-RADS score on both DBT and breast US will be correlated with your histopathology report to assess the diagnostic accuracy of digital breast tomosynthesis compared to breast ultrasound to characterize the mammographic lesion.

ARE THERE ANY RISKS, HARMS DISCOMFORTS ASSOCIATED WITH THIS STUDY?

Medical research has the potential to introduce psychological, social, emotional and physical risks. Effort should always be put in place to minimize the risks. One potential risk of being in the study is the loss of privacy. We will keep everything you tell us as confidential as possible. We will use a code number to identify you in a password-protected computer database and will keep all of our paper records in a locked file cabinet. However, no system of protecting your confidentiality can be absolutely secure, so it is still possible that someone could find out you were in this study and could find out information about you.

Addition of DBT to digital mammography will lead to a slight increase in radiation done by approximately double the dose of the standard two view digital mammography for each breast imaged. This increase in dose is still lower than the maximum acceptable dose in mammography (3mGy per breast).

ARE THERE ANY BENEFITS BEING IN THIS STUDY?

You may not benefit directly as an individual, but the study will aid in development of standardized imaging protocols which are pivotal in imaging of breast cancer. There will be no direct compensation for participating in this study.

WILL BEING IN THIS STUDY COST YOU ANYTHING?

Participation is free and voluntary.

WILL YOU GET REFUND FOR ANY MONEY SPENT AS PART OF THIS STUDY?

There is no expense involved in participating in this study. You will not be compensated.

CONTACTS: WHAT IF YOU HAVE QUESTIONS IN FUTURE?

If you have further questions or concerns about participating in this study, please call or send a text message to the Principal Investigator, Dr. Naaila Kuppuswamy 0712694187.

For more information about your rights as a research participant, you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke.

The study staff will pay you back for your charges to these numbers if the call is for study-related communication.

WHAT ARE YOUR OTHER CHOICES?

Your decision to participate in research is voluntary. You are free to decline participation in the study, and you can withdraw from the study at any time without suffering any negative consequences. You will continue to receive the care and treatment needed even if you do not wish to participate in this study.

CONSENT FORM (STATEMENT OF CONSENT)

Participant's statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with a study counselor. I have had my questions answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.
I understand that all efforts will be made to keep information regarding my identity confidential.
By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.
I agree to participate in this research study: Yes No

Participant printed name: _____

Participant signature / Thumb stamp _____ Date _____

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

Researcher's Name: **_____ Date**: **_____**

Signature _____

Role in the study: **_____**

Witness (*If witness is necessary, a witness is a person mutually acceptable to both the researcher and participant*)
Name _____

Contact information _____

Signature /Thumb stamp: _____
Date: **_____**

Appendix 2: Information and Consent Form (Kiswahili)

STUDY TITLE: A Comparison Between Digital Breast Tomosynthesis And Ultrasound in The Characterization of Mammographic Breast Lesions Using Histopathology as The Gold Standard at Kenyatta National Hospital: A Cross-Sectional matched pairs design.

Kenyatta National Hospital, Nairobi, Kenya

Mtafiti mkuu: Dkt. Naaila Balaraman Kuppuswamy (Chuo Kikuu cha Nairobi)

Watafiti weza: Dkt. Gladys Mwango (University of Nairobi), Dkt. Beatrice Mugi (Kenyatta National Hospital)

UTANGULIZI

Ningependa kukueleza juu ya utafiti unaofanywa na watafiti waliotajwa hapo juu. Madhumuni ya fomu hii ya idhini ni kukupa maelezo unayohitaji ili kukusaidia uamuzi ikiwa Utahusishwa kwa utafiti huu au la. Jisikie huru kuuliza maswali yoyote kuhusu madhumuni ya utafiti, kinachotokea ikiwa unashiriki katika utafiti, hatari na faida iwezekanavyo, haki zako kama kujitolea, na kitu kingine chochote kuhusu utafiti au fomu hii ambayo haijulikani. Tunapojibu maswali yako yote kwa kuridhika kwako, unaweza kuamua kuwa katika utafiti au la. Utaratibu huu unaitwa 'kibali cha habari'. Mara unapoelewa na kukubali kuwa katika utafiti, nitakuomba kusaini jina lako kwenye fomu hii. Unapaswa kuelewa kanuni za jumla ambazo zinatumika kwa washiriki wote katika utafiti wa matibabu: i) Uamuzi wako wa kushiriki ni kikamilifu kwa hiari ii) Unaweza kujiondoa kwenye utafiti wakati wowote bila ya kutoa sababu ya uondoaji wako iii) Kukataa kushiriki katika utafiti hauathiri huduma unazostahili kwenye kituo hiki cha afya au vifaa vingine. Tutakupa nakala ya fomu hii kwa rekodi zako.

Naweza kuendelea? NDIO/LA

UTAFITI HUU UNAHUSU NINI?

Mtafiti aliotajwa hapo juu atawaoji watu ambao wanafanyiwa uchunguzi wa DBT na US ya matiti Lengo la utafiti ni kutambua usahihi wa DBT kulinganishwa na ultrasound ya matiti kuinisha uvimbe ulio onekana kwa matiti kwa kutumia mamografia. wagonjwa 92 watashiriki katika utafiti huu.

NI NINI KITAKACHO FANYIKA UKIAMUA KUHUSIKA KWA UTAFITI HUU?

Ikiwa unakubali kushiriki katika utafiti huu, mambo yafuatayo yatatokea:

- Utapigwa picha ya DBT na ultrasound ya matiti na ku ainisha uvimbe ilionekana na mammagrafia kutumia BI-RADS.
- BI-RADS yako ya mwisho kwenye DBT na ultrasound ya matiti italinganishwa na repoti yako ya histopathology kukadiria usahihi wa DBT ukilinganishwa na ultrasound ya matiti kuanisha uvimbe ulionekana kwenye matiti.

KUNA MADHARA YOYOTE YANAYOTOKANA NA UTAFITI HUU?

Utafiti wa matibabu una uwezo wa kuanzisha hatari za kisaikolojia, kijamii, kihisia na kimwili. Jitihada zinapaswa kuwekwa daima ili kupunguza hatari. Hatari moja ya kuwa katika utafiti ni

kupoteza faragha. Tutaweka kila kitu unachotuambia kama siri iwezekanavyo. Tutatumia namba ya nambari ili kukutambua kwenye darasani ya kompyuta iliyohifadhiwa na nenosiri na tutahifadhi rekodi zote za karatasi kwenye baraza la mawaziri lililofungwa. Hata hivyo, hakuna mfumo wa kulinda siri yako inaweza kuwa salama kabisa, kwa hiyo bado inawezekana kwamba mtu anaweza kujua wewe ulikuwa katika utafiti huu na anaweza kupata habari kukuhusu.
Kuongeza uchunguzi wa DBT kwa mammografia kutasababisha kuongezeka kwa kipimo cha mionzi kwa mara mbili. Kipimo hiki cha mionzi kipo katika kipimo kinachokubalika kwa uchunguzi wa mammogram.

KUNA MANUFAA YOYOTE KWA KUHUSIKA KWA UTAFITI HUU?
Huwezi kufaidika moja kwa moja kama mtu binafsi, lakini utafiti huu utasaidia katika uteuzi utaratibu na mpangilio wa kupima saratani ya matiti. Hutakuwa na fidia moja kwa moja ya kushiriki katika utafiti huu.
KUHUSIKA KWA UTAFITI HUU KUTAGHARIMIA CHOCHOTE?
Hakuna malipo yeyote.
UTAPATA MALIPO YOYOTE AU FIDIA
Hakuna malipo au fidia ili kuhusika kwa utafitu huu
UKITAKA KUULIZA SWALI BAADAYE KUHUSU UTAFITI HUU?
Wasiliana na Mtafiti mkuu, Daktari Naaila Balaraman Kuppuswamy kwa nambari ya simu: +254 712694187 Ama mwenyekiti au katibu msimamizi, utafiti, Hospitali ya Kitaifa ya Kenyatta na Chuo kikuu cha Nairob kupitia nambari 2726300/44102; au kwa anuani uonknh_erc@uonbi.ac.ke. Watafiti watakurejeshea pesa zilizotumika kwa mawasiliano kuhusu utafiti huu.

Appendix 3. Study questionnaire

A COMPARISON BETWEEN DIGITAL BREAST TOMOSYNTHESIS AND ULTRASOUND IN THE CHARACTERIZATION OF MAMMOGRAPHIC BREAST LESIONS USING HISTOPATHOLOGY AS THE GOLD STANDARD AT KENYATTA NATIONAL HOSPITAL

PATIENT BIODATA.

1. Patient X-ray number_____
2. Gender ( ) Male ( ) Female
3. Age: _____
4. Highest level of education: never gone to school ( ) primary ( ) secondary ( ) tertiary college ( ) university ( )
5. Menopause status: pre ( ) During ( ) Post ( ) Not applicable ( )
6. LMP: _____ Not applicable ( )
7. Hormonal contraception: ( ) Yes ( ) No ( )
8. Parity: _____ Not applicable ( )
9. Lactation history: Yes ( ) No ( ) Not applicable
10. Family history of malignancy: _____
11. Reason for mammography: Screening ( ) Diagnostic ( )
12. Clinical symptoms if diagnostic:

	Yes	No
Lump		
Pain		
Nipple discharge		
Nipple retraction		
Nipple retraction		
Skin changes		

DIGITAL MAMMOGRAPHY FINDINGS

13. Breast Density (ACR)

Predominantly fatty (ACR A)	
Scattered fibro-glandular density (ACR B)	
Heterogeneously dense (ACR C)	
Extremely dense (ACR D)	

14. Location of breast lesion.

RUOQ		LUOQ	
RUIQ		LUIQ	
RLIQ		LLIQ	
RLOQ		LLOQ	
Retro areolar			

15. Lesion characterization

Shape	Oval ( ) Round ( ) Irregular ( )
Margins	Circumscribed ( ) Obscured ( ) Micro lobulated ( ) Indistinct ( ) Spiculated ( )
Density	High ( ) Equal ( ) Low ( ) Fat containing ( )

16. Presence of asymmetry:

17. Yes_____ No_____

If yes characterize and localize as asymmetry, focal asymmetry, global, asymmetry, developing asymmetry) _____

Presence of architectural distortion: Yes_____ No_____

Presence of microcalcification: Yes_____ No_____

If yes morphology _____

If yes distribution_____

Assessment category (BIRADS) on digital mammography

_____

DIGITAL BREAST TOMOSYNTHESIS LESION CHARACTERIZATION.

18. Location of breast lesion

RUOQ		LUOQ	
RUIQ		LUIQ	
RLIQ		LLIQ	
RLOQ		LLOQ	
Retro areolar			

19. DBT Lesion characteristics:

Shape	Oval ( ) Round ( ) Lobular ( ) Irregular ( )
Margin	Circumscribed ( ) Obscured ( ) Micro lobulated ( ) Indistinct ( ) Spiculated ( )
Density	High ( ) Equal ( ) Low ( ) Fat containing ( )

20. Presence of architectural distortion: _____

Presence of microcalcifications: Yes_____ No_____

If yes morphology _____

If yes distribution_____

Assessment category (BIRADS) on digital mammography

BI-RADS 0	(need additional imaging or prior exams)
BI-RADS 1	(negative mammogram)
BI-RADS 2	(benign findings)
BI-RADS 3	(probably benign findings)
BI-RADS 4	(suspicious abnormality, biopsy should be considered)
4a	-partially circumscribed mass, suggestive of (atypical) fibro adenoma

	-palpable, solitary, complex cystic and solid cyst
	-probable abscess
4b	-Group amorphous or fine pleomorphic calcifications
	-Non descriptive solid mass with indistinct margins
4c	-New group of linear calcifications
	-New indistinct, irregular solitary mass
BI-RADS 5	(highly suggestive for malignancy)
BI-RADS 6	(known biopsy proven malignancy)

Final assessment BI-RADS Category on DBT_____

BREAST ULTRASOUND LESION CHARACTERIZATION.

21. Location of breast lesion.

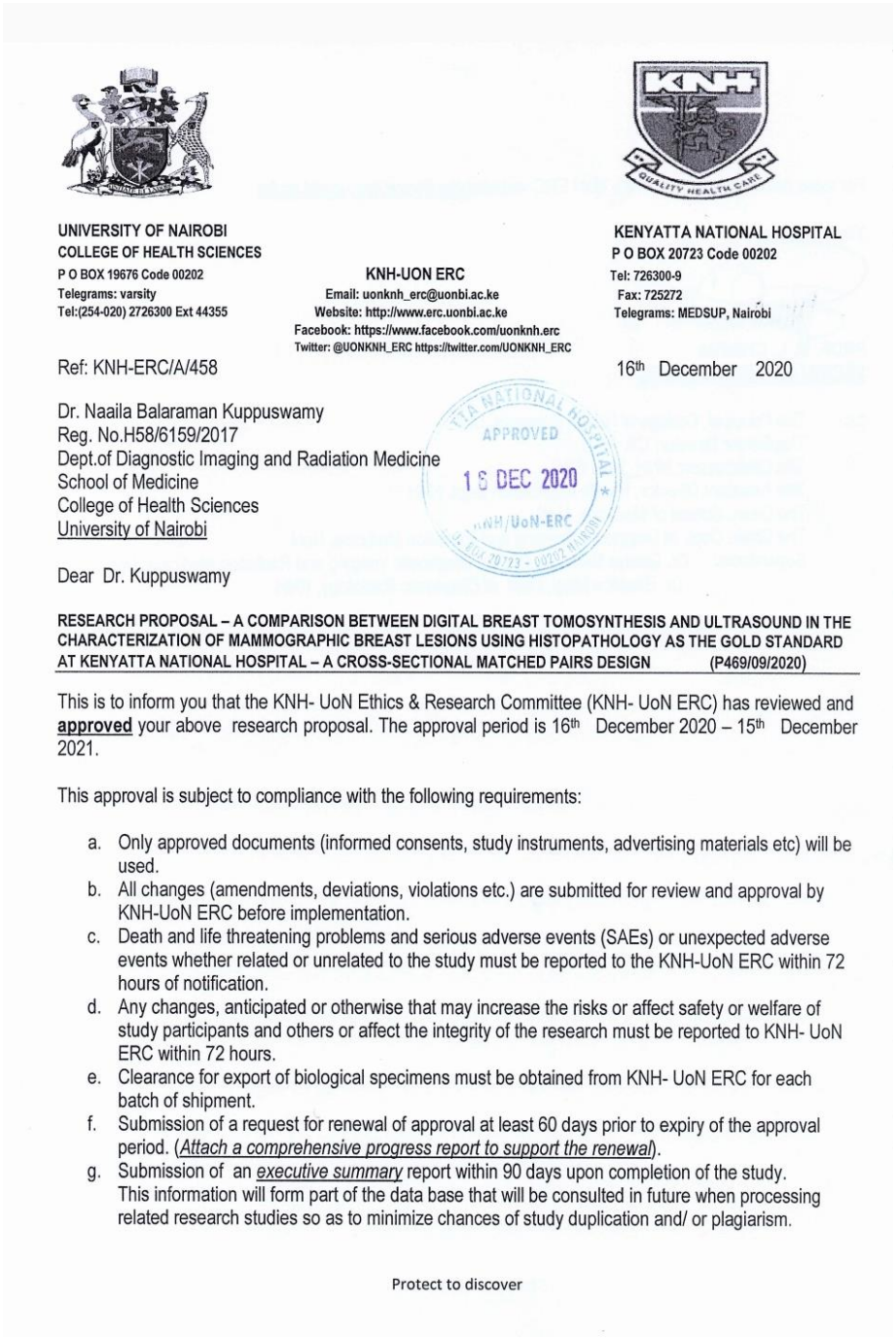
22. US lesion characteristics

Shape	Oval ( ) Round ( ) Irregular ( )
Margins	Circumscribed ( ) Not-circumscribed ( ) Indistinct ( ) Angular ( ) Micro lobulated ( ) spiculated ( )
Orientation	Parallel ( ) Not parallel ( )
Echo pattern	Hypoechoic ( ) Non hypoechoic ( )
Posterior features	No features ( ) Enhancement ( ) Shadowing ( ) Combined pattern ( )
Lesion boundary	Abrupt interface ( ) Echogenic halo ( )
Associated features	Architectural distortion ( ) Skin thickening ( ) Skin retraction ( )
Presence of calcifications	Yes ( ) No ( )

Final assessment (BI-RADS) category on ultrasound_____

Results of histopathology: Malignant ( ) Benign ( )

Appendix 4. ERC approval



UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/458

16th December 2020

Dr. Naaila Balaraman Kuppuswamy
Reg. No.H58/6159/2017
Dept.of Diagnostic Imaging and Radiation Medicine
School of Medicine
College of Health Sciences
University of Nairobi

APPROVED
18 DEC 2020
KNH/UoN-ERC

Dear Dr. Kuppuswamy

RESEARCH PROPOSAL – A COMPARISON BETWEEN DIGITAL BREAST TOMOSYNTHESIS AND ULTRASOUND IN THE CHARACTERIZATION OF MAMMOGRAPHIC BREAST LESIONS USING HISTOPATHOLOGY AS THE GOLD STANDARD AT KENYATTA NATIONAL HOSPITAL – A CROSS-SECTIONAL MATCHED PAIRS DESIGN (P469/09/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 16th December 2020 – 15th December 2021.

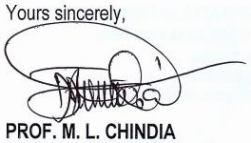
This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

Protect to discover

For more details consult the KNH- UoN ERC website**http://www.erc.uonbi.ac.ke**

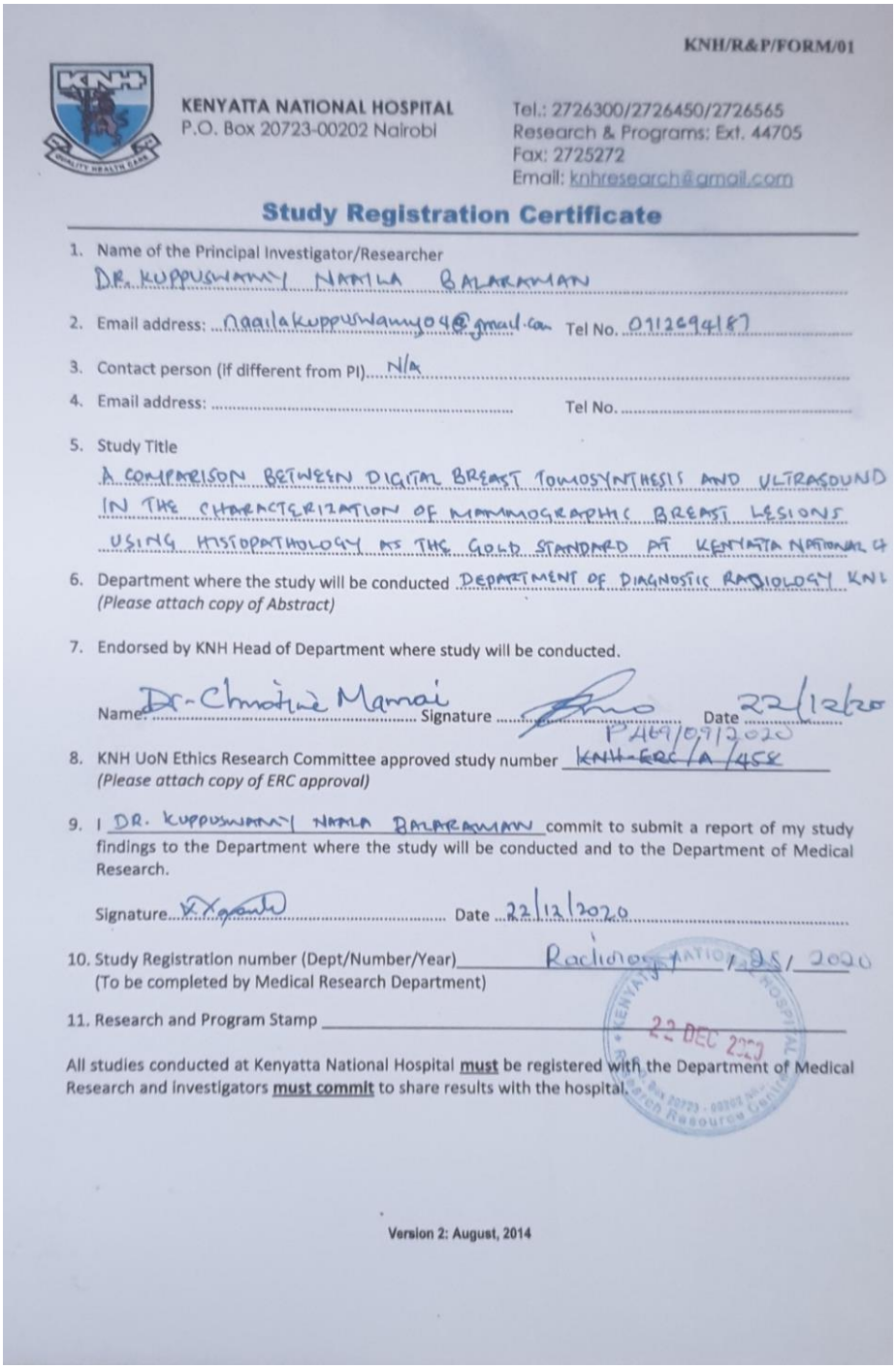
Yours sincerely,



PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information Dept, KNH
The Dean, School of Medicine, UoN
The Chair, Dept. of Diagnostic Imaging and Radiation Medicine, UoN
Supervisors: Dr. Gladys Mwango, Dept.of Diagnostic Imaging and Radiation Medicine, UoN
Dr. Beatrice Mugi, Dept. of Diagnostic Radiology, KNH

Appendix 5. KNH approval



KNH/R&P/FORM/01

KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Tel.: 2726300/2726450/2726565
Research & Programs: Ext. 44705
Fax: 2725272
Email: knhresearch@gmail.com

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   DR. KUPPUSWAMY NAMILA BALARAMAN
2. Email address: ...namilakuppuswamy04@gmail.com Tel No. 0112694187
3. Contact person (if different from PI)... N/A
4. Email address: ..... Tel No. .....
5. Study Title
   A COMPARISON BETWEEN DIGITAL BREAST TOMOSYNTHESIS AND ULTRASOUND IN THE CHARACTERIZATION OF MAMMOGRAPHIC BREAST LESIONS USING HISTOPATHOLOGY AS THE GOLD STANDARD AT KENYATTA NATIONAL H
6. Department where the study will be conducted DEPARTMENT OF DIAGNOSTIC RADIOLOGY KN
   (Please attach copy of Abstract)
7. Endorsed by KNH Head of Department where study will be conducted.
   Name: Dr-Chrotine Mamai Signature ..... Date 22/12/20
   PAG/07/2020
8. KNH UoN Ethics Research Committee approved study number KNH-ERC/A/458
   (Please attach copy of ERC approval)
9. I DR. KUPPUSWAMY NAMILA BALARAMAN commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Medical Research.
   Signature ..... Date 22/12/2020
10. Study Registration number (Dept/Number/Year) Radiology/185/2020
    (To be completed by Medical Research Department)
11. Research and Program Stamp 22 DEC 2020

All studies conducted at Kenyatta National Hospital **must** be registered with the Department of Medical Research and investigators **must commit** to share results with the hospital.

Version 2: August, 2014