ASSESSMENT OF OBSERVER VARIABILITY IN DETERMINING MAMMOGRAPHIC BREAST DENSITY AS PER THE AMERICAN COLLEGE OF RADIOLOGY BIRADS 2013 LEXICON AT KENYATTA NATIONAL HOSPITAL

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2022

DECLARATION

I, Dr. Githaiga Edna Wangeci, declare that the work contained herein is my original idea and has not been presented at any other university or institution of higher learning to the best of my knowledge.

Signature:  **Date:** 18/11/2022

SUPERVISOR'S APPROVAL

This research proposal has been submitted with my approval as a university supervisor.

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LIST OF ABBREVIATIONS

ACR-	American College of Radiology
BIRADS-	Breast Imaging Reporting and Data System
KNH-	Kenyatta National Hospital
ERC-	Ethics and Research Committee
UON-	University of Nairobi
STATA-	Statistical Analysis Software

OPERATIONAL DEFINITIONS

Mammography- A dedicated radiographic technique used for imaging of the breast.

Inter-observer variability- The amount of variation between the results obtained by two or more readers when they assess the same material.

Intra-observer variability- The amount of variation one observer experiences when they review the same material more than once within a specified time duration.

Kilovoltage- Refers to the peak potential applied to the Xray tube which accelerates electrons from the cathode to the anode.

Fibroglandular – Describes the components of the breast tissue which consists of fibrous tissue and glandular tissue.

Breast density- Describes the amount of the fibroglandular component in a woman's breast relative to the fat content.

ABSTRACT

Background

Breast density is a well-known and proven independent risk factor for breast cancer and can significantly affect the sensitivity of screening mammograms. Mammographic breast density is thus great importance in the evaluation of a mammogram because increased breast density is known to increase the risk of individual breast cancer (1)

Analysis of breast density is done through the ACR- Birads lexicon 2013, which categorizes breast density into four categories A-D A- Almost entirely fatty, B- scattered areas of fibroglandular density, C- heterogeneously dense, which may obscure small masses and D- extremely dense, which lowers the sensitivity of mammography.

Due to the subjective nature of the visual assessment during categorization, differences may arise when assessing the breast density between two observers. It is important to assess the degree of agreement or variability as this affects the reproducibility of the report.

Aim

The study aimed to evaluate and record the degree of inter and intra observer variability when assessing the mammographic breast density using the Breast Imaging Reporting and Data System (BIRADS), as defined by American College of Radiology.

Methodology

Cross-sectional study was carried out at Kenyatta National Hospital, mammography department of Radiology over a period of one year. Four radiologists were required to review mammograms that were of diagnostic value and classify the breast density based on the ACR classification 5th edition. After an interval of one month, they were asked to review the same mammograms again. Mammographic density category for each mammogram by each radiologist was recorded.

Statistical Analysis

The intra-observer variability was calculated for each radiologist and reported as weighted kappa values and 95% confidence intervals.

Fleiss-Cohen Kappa coefficients and their corresponding 95% confidence intervals were used to calculate the inter-observer variability.

The levels of agreement were assigned a kappa value between 0.0-1.0 where 0.0 was considered as no agreement and 1.0 was considered perfect agreement.

Results

There was moderate overall inter-observer variability both at baseline and after the one-month review with kappa values being 0.49(95% CI 0.43,0.59) and 0.43 (95% CI 0.38,0.61)) respectively when using the ACR BI-RADS 2013 lexicon to assess breast density. The intra-observer variability was substantial with kappa values ranging from 0.61(95% CI 0.48- 0.72) to 0.77 (95% CI 0.67-0.87).

Conclusion

There was a moderate level of inter- and intra- observer variability demonstrated when assessing mammographic breast density but a substantial level of individual intra-observer variability.

1.0 CHAPTER ONE: INTRODUCTION AND BACKGROUND

Breast density describes the amount of fibro glandular tissue in a woman's breast relative to the fat content. The hyperdense breast tissue consists of glandular components of epithelial origin, the terminal ductal lobular units and ducts. It also contains stromal components which include supportive fibrous connective tissue found in the intra and interlobular stroma (2)

Mammographic breast density is of great importance in the evaluation of a mammogram because increased breast density is known to increase the risk of individual breast cancer (1), it is an additional risk of regional breast cancer recurrence (3) as well as increased interval cancers and poorer prognosis (4). In addition, dense fibroglandular tissue affects mammographic sensitivity since it can obscure a lesion (5). Therefore, women who have dense breasts should be recognized and recommended for further screening imaging with ultrasonography or MRI to avoid missing out on important breast lesions. The use of MRI for screening is dependent on the defined levels of risk as defined by the American Cancer Society. (6). This could either be high or intermediate risk. Dense breast at mammography is considered intermediate risk and there is no sufficient data for or against the use of MRI for screening in such groups.

Despite the challenges that arise with dense breast, mammography is still the recommended imaging modality used for screening women. There are various ways described to characterize breast densities which can either be quantitative or qualitative. Some of these were described by Wolfe (7), Tabar (8), Boyd et al (9). The most used method is the qualitative analysis using the BIRADS lexicon which was developed by the American college of Radiologists. The main aim being to standardize aspects of reporting breast imaging modalities, one of the of which is mammographic breast density.

The accuracy of screening mammography is influenced by factors such as the procedures for reviewing mammograms, characteristics of the individual breast, and the knowledge and skill of radiologists. Due to the subjective nature of the visual assessment during categorization, differences may arise when assessing the breast density between two observers. Double reading of mammograms has been described to yield better diagnostic accuracy by several authors(10) and has also been incorporated in some guidelines such as European Commission guidelines for quality assurance in breast cancer screening and diagnosis (11). Due to human resource constraints, it is common practice that mammographic reading has been done by one radiologist in our local setting. Our national cancer screening guidelines of 2018 (12) are silent on the issue of single versus double reading. The aim of this study is to come up with local quantified evidence of observer variability in assigning mammographic density category which is an integral part of mammographic interpretation. It is also important to assess the degree of agreement or variability as this affects the reproducibility of the report.

Artificial intelligence has gained traction in the assessment of mammographic breast density initially with computer aided diagnosis (CAD) and now recently with deep learning algorithms. (13)Various studies carried out by Le Boulc’h (14) and Lehman (15) found that Mammographic breast density assessment using an artificial intelligence model and a radiologist was almost similar with kappa value of 0.79 (95% CI 0.73-0.84) and 0.67(95% CI 0.66-0.68) respectively indicating substantial agreement. The increasing use of artificial intelligence in breast imaging will offer an objective and efficient way of assessing mammographic breast density among breast radiologists. It will also help reduce the variations and inconsistencies that may exist with the qualitative assessment.

2.0 CHAPTER TWO: LITERATURE REVIEW

2.1 Anatomy

The breast is an organ located on the anterior chest wall over the pectoralis muscles between the third and seventh rib. It extends from the lateral sternal edge to the mid axillary line with axillary extension also known as the tail of Spence. The breast shape and volume is affected by factors such as age, genetics and hormonal stimulation. (16)

The breast consists of the skin and nipple-areolar complex, adipose tissue, glandular portion and connective tissue. The glandular part of the breast has 15-20 lobes which are arranged in a radial fashion around and behind the nipple which drain through the main lactiferous ducts, defining a segment. Each segment consists of lobules and each lobule is drained by a terminal duct which has saccular dilatations that form acini. The terminal duct and the lobule form the terminal duct lobular unit which is the functional unit of the breast and the most important diagnostic element. (17)

Breast density illustrates the amount of the fibroglandular component in a woman's breast relative to the fat content. The hyperdense breast tissue consists of glandular components of epithelial origin, the terminal ductal lobular units and ducts. It also contains stromal components which include supportive fibrous connective tissue found in the intra and interlobular stroma (2)

Breast density is a key feature during the assessment and reporting of breast imaging because there is wide knowledge that breast density increases the risk of occurrence of breast cancer. A study by V. Tesic et al on mammographic density and estimation of breast cancer risk in intermediate risk population showed that mammographic breast density was an important factor associated with breast cancer development.(1). (18)

There is also a higher risk of incidence of recurrent breast cancer among women with mammographically dense breast as demonstrated by C.C. Park et al (2009). The study showed that high mammographic breast density conferred a greater rate of local relapse of breast cancer among women who underwent breast conserving surgery and radiotherapy among non-obese women. (3)

In addition, breast density affects mammographic sensitivity in detection of pathologies. A study by I. Saarenmaa et al on the significance of age and breast density on mammographic sensitivity showed that mammographic breast density is an independent factor that affects the sensitivity of a mammogram (4). Regardless of the limitations associated with sensitivity of a mammogram associated with dense breast, it is important that the breast density finding be reproducible so as not only to inform the patient of their increased risk of breast cancer but also to determine which patients may benefit from additional screening methods. (19)

2.2 Factors affecting breast density.

Breast density is influenced by various factors which include body mass index, age, ethnicity, tamoxifen therapy, hormone replacement therapy, pathology (cancer and inflammation), pregnancy and lactation. Breast density decreases with increasing body mass index (20) and increasing age (21) (paradoxically, these two factors increase breast cancer risk). Ethnicity affects breast density with Caucasian women having higher breast density compared to African-American women and Latin women (22) (23)

Use of HRT increases the prevalence of the dense patterns and potentially may adversely affect the effectiveness of mammographic sensitivity (24) Tamoxifen use in women with an increased risk of breast cancer has been associated with a reduction in breast density during the first 18 months of treatment.(25)

Systemic diseases may affect breast density. Congestive heart failure causes bilateral increase in breast density (26) Unilateral breast oedema may cause increased breast density in pathologies such as inflammatory breast cancer, leukaemia, post radiation changes, poor lymphatic drainage and mastitis (27)

2.3 Breast Imaging Modalities

There are various radiologic ways of imaging the breast which include mammography, ultrasonography and MRI but mammography is preferred for screening (28). Ultrasonography is mostly used as a complementary imaging modality to mammography and is rarely advisable for use in isolation for screening in breast cancer(17). Breast MRI has been shown to have the highest sensitivity in detection of breast cancer and its use in invaluable in breast imaging. It is also taking a huge role in screening as it has been shown to detect cancers earlier than mammography (29). Due to the prohibitive costs associated with MRI, mammography remains widely used as a standard screening tool for breast cancer.

2.3.1 Principle of Mammography

Mammography screening is specific (94% to 97%), sensitive (77% to 95%), and tolerable to many women. The breast composition results in the tissues having relatively similar densities and exceedingly small attenuation differences on X-Ray. Breast pathology and normal tissues also have close to similar attenuation properties. The use of mammography applies the principle that use of low kilovoltages techniques amplifies radiographic tissue contrast by maximising the differences in tissue absorption (17). The radiological female breast appearance varies radiologically among individuals and with age because of variances in composition and attenuation properties of fat and epithelial and stromal tissues. Fat appears radiolucent thus dark while the epithelium and stromal components appear radio dense thus bright on the mammogram.(30)

2.3.2 Technique and views in Mammography

Mammography has evolved over the years from its onset with direct exposure film mammography to xeromammography to screen-film mammography to the current era of full-field digital mammography and digital breast tomosynthesis.(31)

With the evolution of the mammography, the techniques of acquiring the mammograms have evolved with the introduction of breast compression. Compression began with screen film to ensure uniform spread out of the breast tissue permitting better visualization.

The process of acquiring a mammogram involves placing and compressing the patient's breast between two flat compression plates of the mammography machine and using X-rays with low kilovoltage to acquire the images which gives good soft tissue resolution.

Routine mammographic views include Craniocaudal views and Medial lateral oblique views. These views are complementary and are used to image the breast with minimal radiation dose to the patient. Additional tomosynthesis can be done to overcome tissue superimposition in especially dense breast.(32)

2.3.2 How to Measure Density

Breast density measurement is broadly divided into three ways 1) through the mode of assessment which can either be fully or semi-automated or visual assessment. 2) by assessing the area or volume of the breast density and 3) through qualitative and quantitative method (33). These methods of measurement of mammographic breast density have evolved over the years.

The BIRADS lexicon is a visual qualitative method of breast assessment. It was first developed by the American College of Radiology, the first publication being in 1993. The second, third, and fourth publications were released in 1995, 1998, and 2003 respectively with the latest one (fifth edition) being released in 2013. The aim was to bring a widely accepted standard that can be used in the clinical reporting of mammograms that has many aspects among which is mammographic breast density (34). This is done through a visual observation where the overall attenuation of the fibroglandular tissue is assessed to determine the possibility of masking or obscuring a lesion.

Four categories of breast density have been described and are listed alphabetically from a-d. There is considerable inter and intra observer variability between adjacent categories as compared to categories at the extremes (34). If there are differences in the breast densities of the two breasts, the overall category is assigned to that matching the denser breast.

Table 1:Breast Tissue

Breast Composition Categories

A.	The breasts are almost entirely fatty.
B.	There are scattered areas of fibroglandular density.
C.	The breasts are heterogeneously dense, which may obscure small masses.
D.	The breasts are extremely dense, which lowers the sensitivity of mammography.

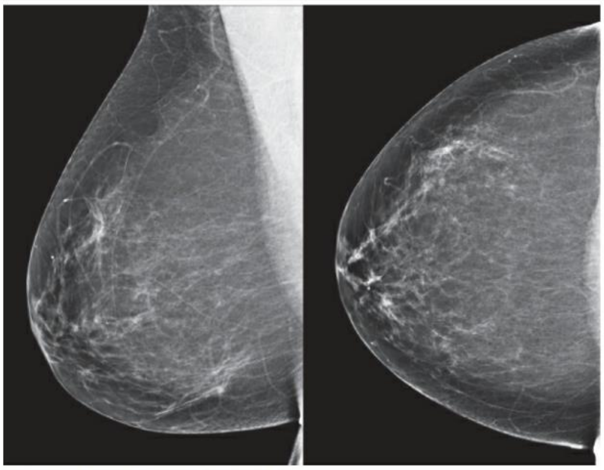


Figure 1: The Breasts are almost entirely Fatty(34)

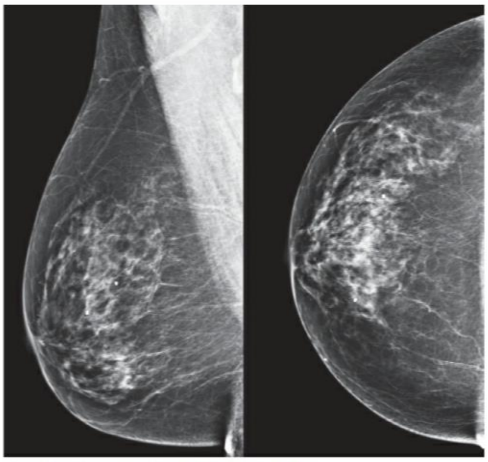


Figure 2:There are scattered areas of fibroglandular tissue(34)

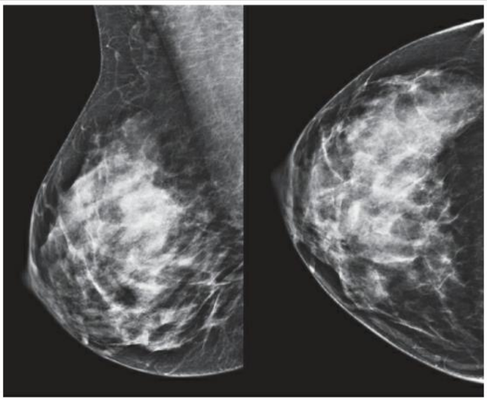


Figure 3:The breast are heterogeneously dense which may obscure small masses(34)

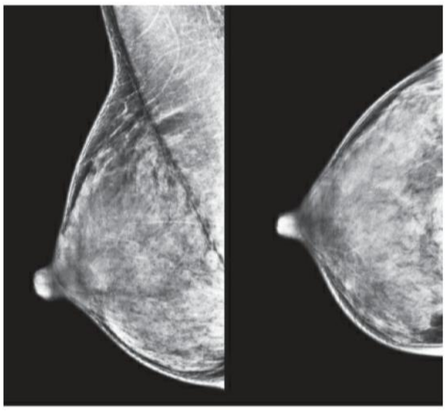
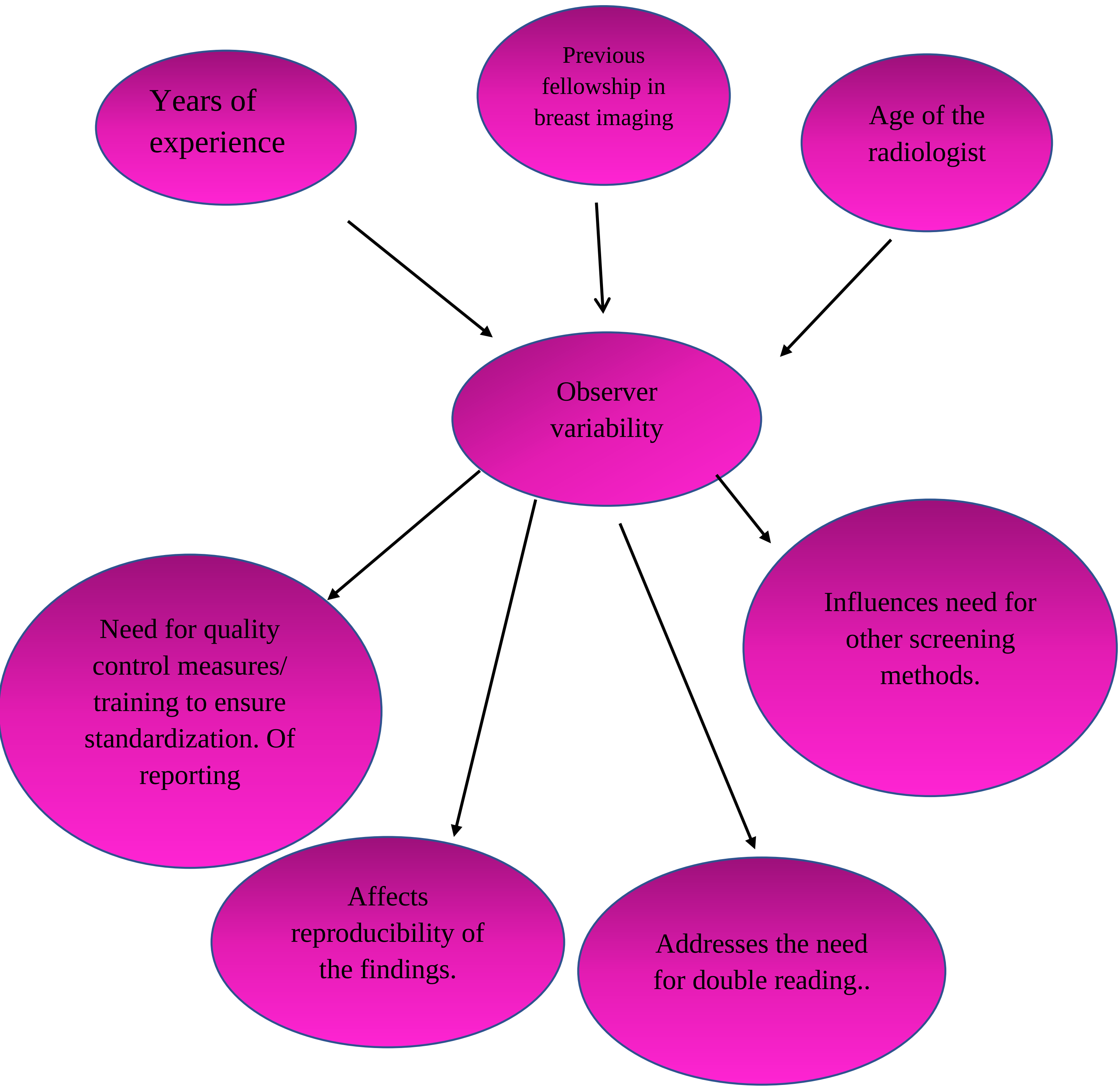


Figure 4:The breasts are extremely dense which lowers the sensitivity of mammograms(34)

Various studies(35), (36), (37) have shown moderate levels of observer variability when using the BIRADS classification to assess breast density. This has resulted in a rise in interest in the use of other methods such as semi-automated and automated methods quantitative methods using a computer-assisted technique of measuring percentage mammographic densities.

Studies done previously have shown moderate agreement with most variability occurring between ACR B and ACR C. A study by Berg (35) showed moderate observer concordance in a study where five radiologists who did not have training on BI-RADS assessment reviewed 103 screening mammograms. Furthermore, Ciatto (38) found a kappa value of 0.54 when using the ACR BI-RADS classification, when 12 radiologists with experience in breast imaging evaluated 100 mammograms. A newer study by Gemici et al (39), using 330 mammograms reviewed by one radiologist with experience in breast imaging, showed significant intra observer agreement (k=0.77). No local studies have been done with regards to this topic.

2.3 Conceptual Framework



2.4 Study Justification

Mammography is the investigation of choice used in breast screening. It plays a major role in the early diagnosis of breast cancer. With the rising awareness among patients and the increase in prevalence of breast cancer cases both locally and internationally, there is an increasing use of mammography. Breast density being a known risk factor for development of breast cancer (1)(18), is one of the features analysed in a mammogram. Increasing breast density decreases the efficacy of a breast mammogram and increases the risk of small lesions being masked. Since categorization of mammographic breast density is done through visual assessment, there may be variability seen with description of adjacent breast densities (35)(36)(37)(39). The variability raises concern that a single patient may receive a different breast density category. This study sought to establish and quantify observer variability in breast mammographic density categorization. This may impact in policy making especially regarding the value of double reading of mammograms. In addition to that it gave insight into the reliability and reproducibility of the visual assessment. The study also aimed to sensitize, through Kenya Association of Radiologists these findings.

No Kenyan studies have been done to assess inter- and intra-observer variability to the best of our knowledge. This is coupled with the fact that sub-specialization in breast imaging in Kenya is limited, with the number of radiologists in that sub-specialty being only two.

2.5 Research Question

What is the inter and intra observer variability of mammographic breast density using the ACR BI-RADS lexicon at Kenyatta National Hospital?

2.6 Hypothesis

There is no inter and intra-observer variability in the assessment of mammographic breast density.

2.7 Study Objectives

2.7.1 Broad

Assess and compare inter- and intra-observer variability of mammographic breast density using the ACR-BI-RADS lexicon

2.7.2 Specific

- **a)** To assess the inter-observer variability in assigning mammographic breast density
- **b)** To assess the intra-observer variability in assigning mammographic breast density
- **c)** To compare inter and intra observer variability of mammographic breast density.

3.0 CHAPTER THREE: METHODOLOGY

3.1 Study Design

This was a cross-sectional study of four radiologists evaluating mammograms of adult women seeking mammography screening services at the Kenyatta National Hospital. Four out of seven radiologists with at least five years' experience in breast imaging who were willing and available to review the images twice within a period of one month were recruited.

3.2 Study Setting

The study was based at the Radiology Department of the Kenyatta National Hospital (KNH), which is a tertiary teaching and referral hospital in Nairobi, Kenya, and the largest hospital in East Africa. The study was done using the GE Essential Senographe Digital Mammography Unit, made in France in 2013 which is installed at the radiology department of the Hospital. The study was undertaken over a period of one year between September 2020- September 2021

3.3 Study Population

The mammograms were interpreted by 4 radiologists with at least 5 years' experience and who were involved in reporting of clinical and screening mammograms. The mammograms were included consecutively for all adult female patients (≥18 years) in the radiology department screened for breast cancer through mammography. The hospital has approximately 600 female patients seeking mammography every year which is 50 mammograms per month. Approximately 30% of those met the eligibility criteria translating to 15 mammograms Therefore, the estimated duration of the data collection was 5 months.

3.3.1 Inclusion Criteria

I. Radiologists with at least 5 years' experience in breast imaging who consent to participant in the study and are available to review the mammograms a month later.

II. All mammographs with good technique and exposure factors as per ACR quality guidelines and checklist (40). (41)This entails use of proper compression techniques, use of low kilovoltage and low tube current which results in maximization of contrast-to-noise ratio.

3.3.2 Exclusion Criteria

I. Radiologists not available to review of the mammograms a month later to assess intra-observer variability.

II. Mammograms of women with history of previous breast surgeries

III. Mammograms of women with history of chemotherapy

IV. Mammograms of women with breast implant or cosmetic procedures or foreign bodies

V. Mammograms with distracting pathology that cause asymmetry in the breast size and tissue.

3.4 Sample Size Determination

The study aimed to compare inter- and intra-observer variability of mammographic breast density among four radiologists with a Likert (ordinal) scale of four (breast composition categories – A, B, C and D). We hypothesized the minimum value for the Cohen's kappa coefficient as 0.7 (K_2=0.7) with an assumed kappa coefficient of 0.5 (K_1=0.5). (42)

$$n = \left(\frac{sd_0 \cdot z_{1-\alpha} + sd_1 \cdot z_{1-\beta}}{\kappa_1 - \kappa_0} \right)^2$$

When the power and alpha were pre-specified at 80.0% and 0.05 respectively, a minimum sample of 76 mammograms were required for the detection of a minimum value of kappa coefficient of 0.7 while holding an assumption that the proportion of ratings in agreement by all radiologists in each category was assumed to be directly proportional to one another (43).

3.5 Recruitment and Consenting Procedures

Four qualified radiologists with at least 5 years' experience who were involved in reporting of clinical and screening mammograms at the Radiology Department of the Kenyatta National Hospital (KNH), were purposively identified and requested to take part in the study. Consent from the radiologists to be included in the study was sought by filling and signing an informed consent form (appendix A). Waiver of patient consent was sort because the mammograms used were reviewed retrospectively from the database.

3.6 Data Collection Procedures

Full digital mammograms that met the technical and exposure factor (that is adequate compression techniques, use of low kilovoltage and low tube current) and were of diagnostic quality were chosen. Both craniocaudal and Mediolateral oblique views were obtained.

The readers were blinded to the patient's age and clinical information. The readers were asked to classify the breast density based on the ACR classification 5th edition (34)(44). Cases were then reviewed after one month to evaluate intra-observer variability and the evaluating order was changed to reduce memory bias. If there is an asymmetry of breast density, the one with a higher breast density was chosen. The budget and timelines are available in the appendices (D and E respectively)

3.7 Variables

The dependent variable were breast density based on the ACR classification 5th edition. The independent variables were sociodemographic (age, level of experience) data.

3.8 Data Management

Data on classification of the breast density based on the ACR classification 5th edition was entered in a data capture form. All data capture tools were collated daily and stored in a lockable cabinet for security reasons by the researcher. Data was entered in Microsoft Excel spreadsheet and stored electronically as a password protected file. A password protected backup copy was stored in cloud.

3.9 Data Analysis

The Excel dataset was exported to STATA statistical software version 16 for analysis (44). Descriptive statistics (medians, means, standard deviations and inter-quartile ranges) were used to summarize continuous variables including age. Proportions were used to summarize categorical variables like ACR BIRADS classification 5th edition criteria. Presentation were done using tables and bar graphs.

The intra-observer agreement was computed for each radiologist assessing breast density using ACR BIRADS 5th edition criteria and reported as weighted kappa values and 95% confidence intervals (CIs).

The inter-observer variability between the radiologists on the ACR classifications was computed by calculating the overall percentage of agreement (concordance). The difference between the rate of agreement (concordance) that was observed and the rate of agreement that was expected purely by chance was measured using Fleiss-Cohen's weighted kappa (k) due to the ordinal scale of breast density (from A to D) and use of multiple observers (45). The 95% confidence interval (CI) was estimated for κ.

The strength of κ coefficient of <0 was considered poor, 0-0.20 as slight, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial while more than 0.80 corresponded to an almost perfect agreement, as per the scale proposed by Landis and Koch (46). Statistical significance was interpreted at 5% level (p value < 0.05).

3.10 Quality Assurance Procedure

The mammograms were acquired by a technologist with minimum 5 years' experience and this ensured that similar compression techniques were achieved. The mammogram images were examined to ensure that they are devoid of artefacts.

To ensure standardization when reporting the mammographic density, a brief oral training session was held for each radiologist that also included availing an ACR atlas images and as well as the 2013 edition of the ACR guidelines. Memory bias was mitigated by re-ordering the images when reviewing the images after one month. Non-response bias was mitigated by ensuring that the respondents who would not be available after one month to review the images were not selected. Volunteer bias was also mitigated by ensuring only the radiologists with at least five years' experience in breast imaging were chosen At this stage state how any potential bias during the study was mitigated.

3.11 Ethical Considerations

Ethical approval was obtained from Kenyatta National Hospital/University of Nairobi ethics and research committee (KNH/UoN ERC). Waiver of informed consent for use of routinely collected demographic, clinical data of patients seeking mammography screening as well as the mammograms available in the database was obtained from the ERC.

Confidentiality was maintained throughout the study period while handling patient information by ensuring that codes were used in place of patient names among other measures. Confidentiality of the reporting radiologists and the patient was ensured through pseudonymisation of their identity.

Permission to conduct the study was obtained from the hospital administration. No additional financial cost were incurred by the participant for participating in the study.

3.12 Study Results Dissemination plan

The information and data from the study will be disseminated through a thesis report, manuscripts and conference presentations to relevant stakeholders to emphasize the importance of breast density in the assessment of mammograms.

CHAPTER 4: RESULTS

Table 2. Sociodemographic characteristics of reporting radiologists (n=4)

Table 2 shows the socio demographic characteristics of the reporting Radiologist. The median age of the radiologist was 39 years IQR (36,46). 3 radiologists were female whist 1 was male. The median year of radiologist experience was 6 years IQR (5,13)

Variable	**Frequency/Median**	**%/IQR**
Age	39	36,46
Sex		
Female	3	75%
Male	1	25%
Years of experience as a radiologist	6	5,13

Table 3: Age and level of experience of the reporting radiologist

Rater	**Age**	**Years of Experience**
Radiologist A	36	5
Radiologist B	42	7
Radiologist C	36	5
Radiologist D	56	30

Fig.1. Percent of BIRADS breast density reported by radiologists at Baseline

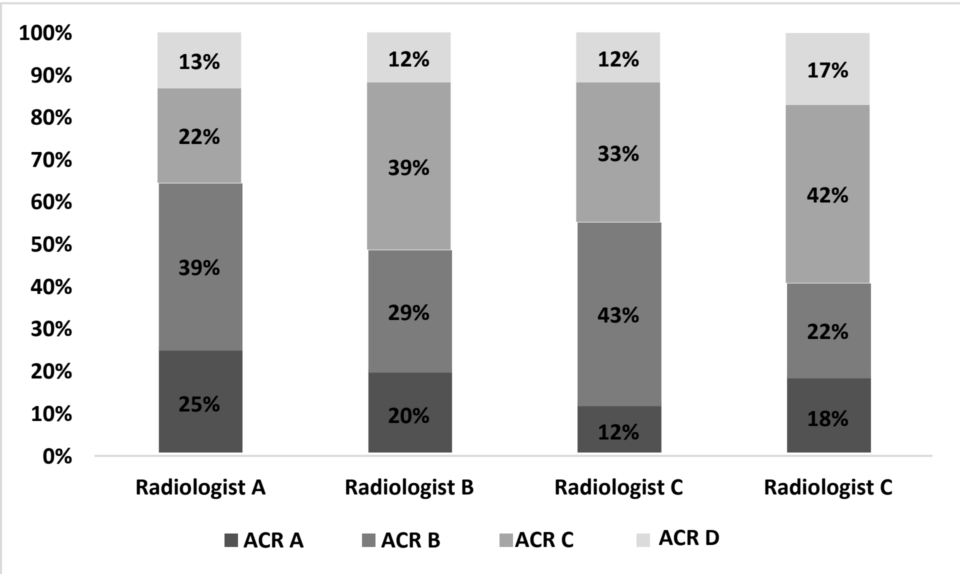


Fig.1. Percent of BIRADS breast density reported by radiologists at baseline

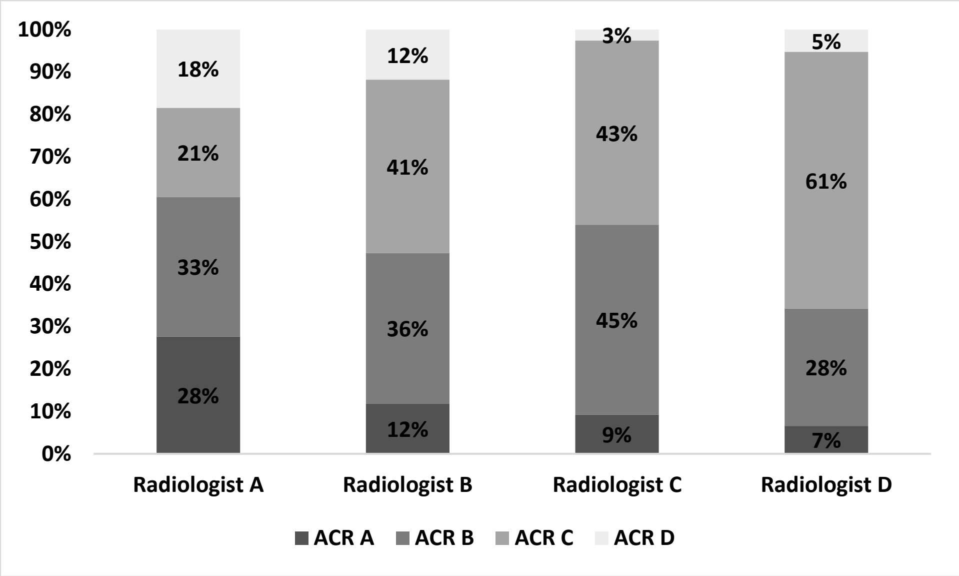


Fig.2. Percent of BIRADS breast density reported by radiologists after one month

TABLE 3: Inter-observer agreement in breast density based on the ACR classification 5th edition between pairs of radiologists and overall agreement among all radiologists at Baseline

Pairs of observers	Weighted kappa value	P-value
A, B	0.644 (0.53,0.75)	<0.0001
A, C	0.662 (0.58,0.76)	<0.0001
B, C	0.664 (0.54,0.78)	<0.0001
B, D	0.639(0.52,0.75)	<0.0001
A, D	0.601(0.48,0.72)	<0.001
C, D	0.638 (0.51,0.76)	<0.0001
Weighted overall kappa (A, B, C, D)	0.49(0.43,0.59)	<0.0001

TABLE 4: Inter-observer agreement in breast density based on the ACR classification 5th edition between pairs of radiologists and overall agreement among all radiologists after one month

Pairs of observers	Weighted kappa value	p-value
A, B	0.62(0.52,0.74)	**<0.0001**
A, C	0.57(0.47,0.67)	**<0.0001**
B, C	0.68(0.56,0.80)	**<0.0001**
B, D	0.60(0.46,0.73)	**<0.0001**
C, D	0.55(0.41,0.70)	**<0.0001**
A,D	0.44(0.28,0.52)	**<0.0001**
Weighted overall kappa (A, B, C, D)	0.43 (0.38,0.61)	**<0.0001**

TABLE 5: Intra-observer agreement in breast density based on the ACR classification 5th edition among Radiologists

Radiologists	Kappa value (95% CI)	P value
A	0.75(0.66,0.84)	<0.0001
B	0.77(0.67,0.87)	<0.0001
C	0.61(0.49,0.74)	<0.0001
D	0.61(0.48,0.72)	<0.0001
Overall	0.46(0.32,0.57)	<0.0001

Table 6: Weighted kappa values for each ACR BI-RADS breast density category reported by the four radiologists at Baseline

ACR breast density category	Weighted kappa value	95% CI	P value
A	0.63	0.54,0.72	<0.0001
B	0.32	0.23,0.41	<0.0001
C	0.44	0.35,0.54	<0.0001
D	0.69	0.60,0.78	<0.0001

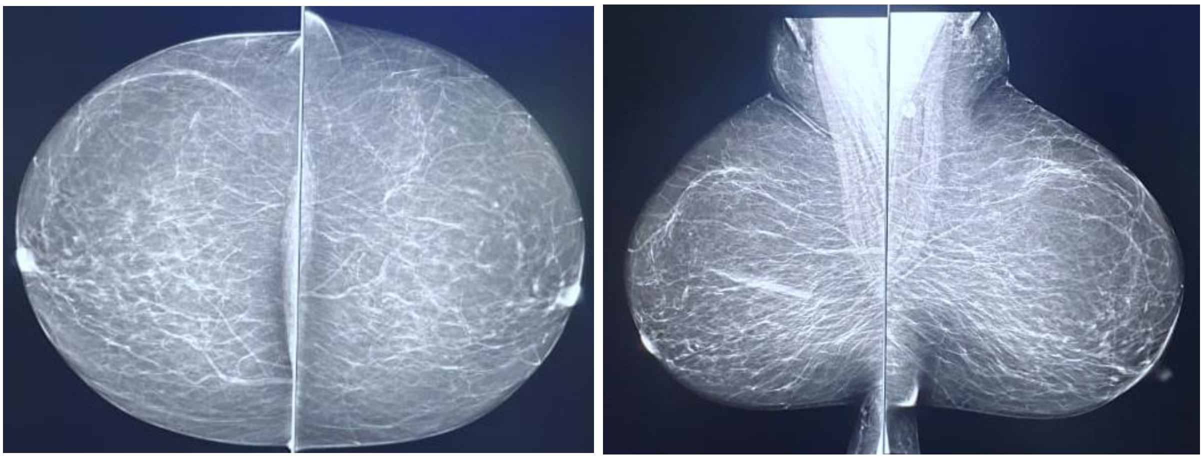
Table 7: Weighted kappa values for each ACR BI-RADS breast density category reported by the four radiologists after one month

ACR breast density category	Weighted kappa value	95% CI	P value
A	0.47	0.37,0.55	<0.0001

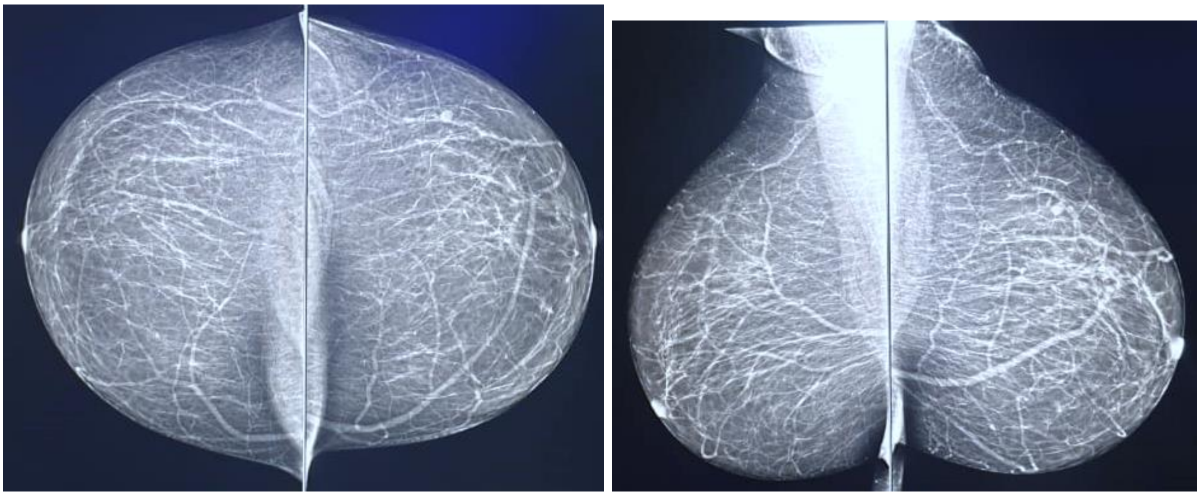
B	0.39	0.30,0.48	<0.0001
C	0.44	0.35,0.54	<0.0001
D	0.42	0.60,0.78	<0.0001

ILLUSTRATIONS OF SAMPLE CASES

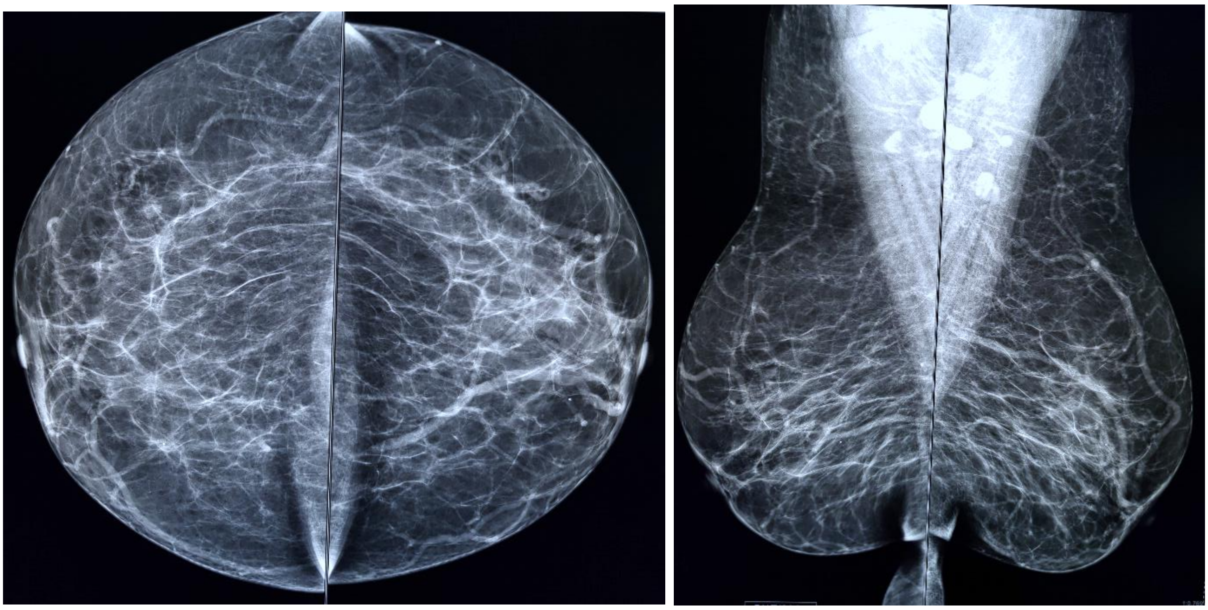
Case 1. Fig 3 Sample craniocaudal and medial lateral oblique mammogram images obtained during the study showing the breasts are almost entirely fatty.



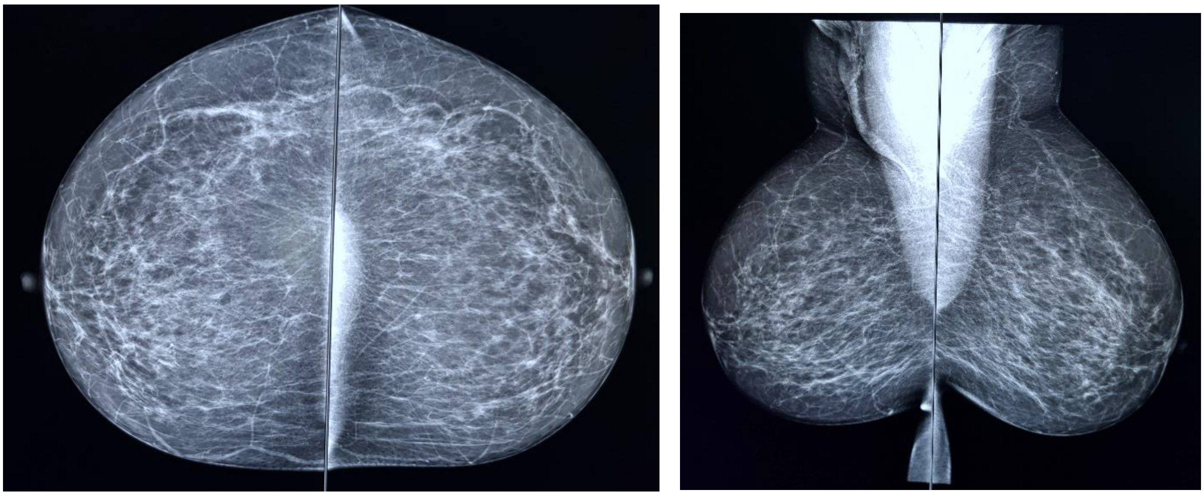
Case 2. Fig 4 Sample craniocaudal and medial lateral oblique mammogram images obtained during the study showing the breasts are almost entirely fatty.



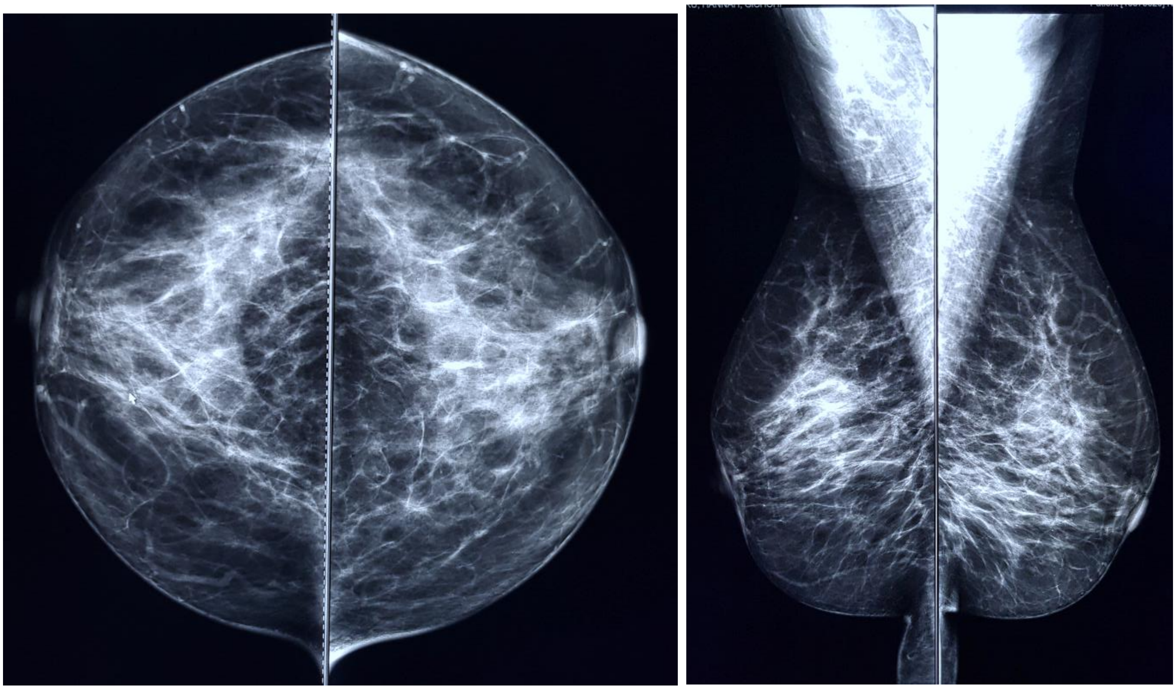
Case 3. Fig 5 Sample craniocaudal and medial lateral oblique mammogram images obtained during the study showing the breasts are scattered areas of fibroglandular density.



Case 4. Fig 6 Sample craniocaudal and medial lateral oblique mammogram images obtained during the study showing the breasts are scattered areas of fibroglandular density.

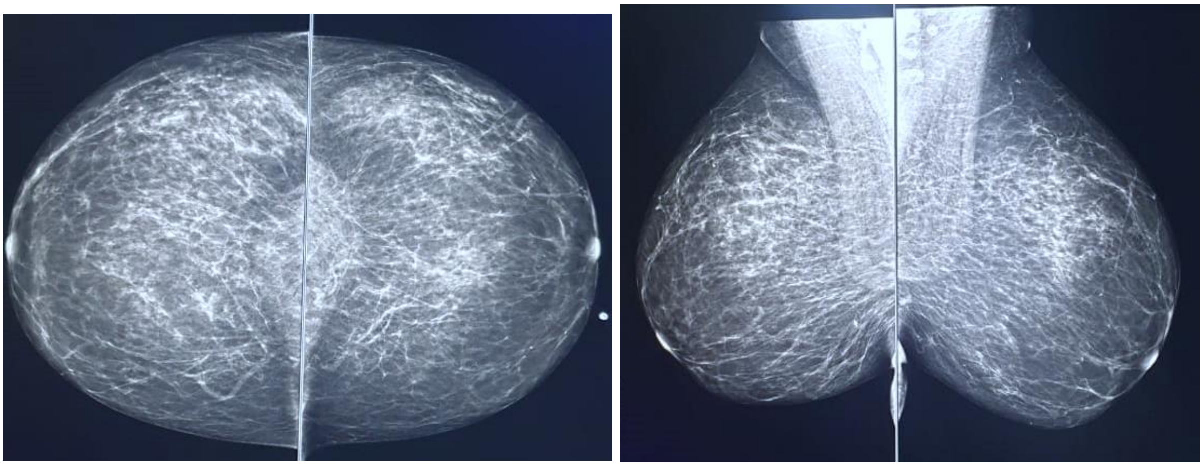


Case 5. Fig 7 Sample craniocaudal and medial lateral oblique mammogram images obtained during the study showing the breasts are heterogeneously dense, which may obscure small masses.

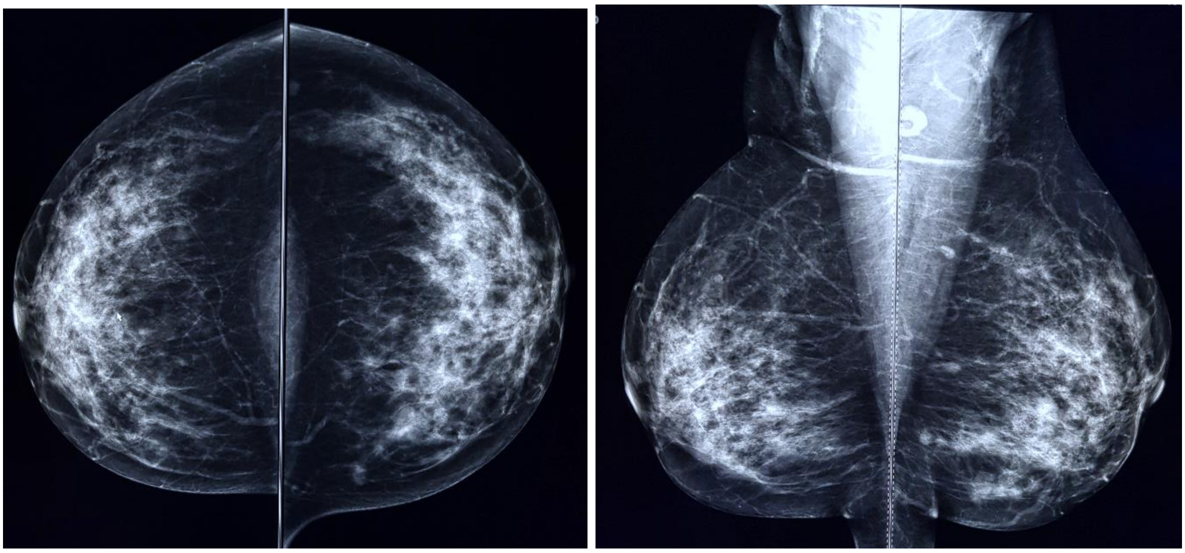


C

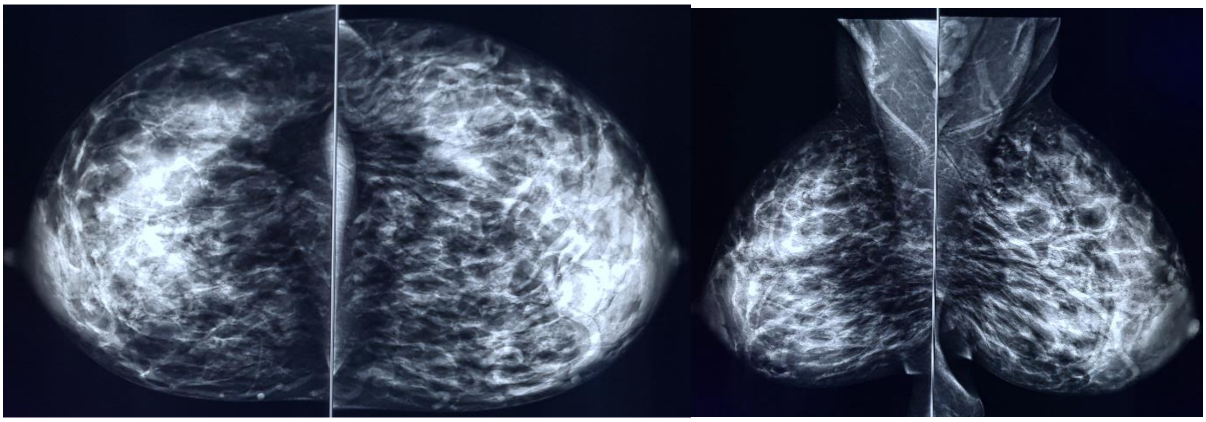
Case 6. Fig 9 Sample craniocaudal and medial lateral oblique mammogram images obtained during the study showing the breasts are heterogeneously dense, which may obscure small masses.



Case 7. Fig 10 Sample craniocaudal and medial lateral oblique mammogram images obtained during the study showing the breasts are extremely dense, which lowers the sensitivity of mammography.



Case 8. Fig 11 Sample craniocaudal and medial lateral oblique mammogram images obtained during the study showing the breasts are extremely dense, which lowers the sensitivity of mammography.



CHAPTER 5:

5.1 DISCUSION

In this study we demonstrated moderate overall inter-observer variability both at baseline and after the one-month review with kappa values being 0.49(95% CI 0.43,0.59) and 0.43 (95% CI 0.38,0.61)) respectively when using the ACR BI-RADS 2013 lexicon to assess breast density. Additionally, all four readers showed moderate agreement when compared in pairs both at baseline and after the one-month interval

Previous studies done by Berg (35)and Ciatto (36) also showed moderate agreement. Similar to this study, the radiologists in the study done by Berg (35) were not specially trained in using the BI-RADS lexicon. Additionally, the radiologists in Ciatto (36) were radiologists with breast imaging experience though they did not have a long experience with using the BI-RADS lexicon. Of importance to note is that the BI-RADS lexicons used Berg (35) and Ciatto (36) were different from this study that is ACR BI-RADS 1995 lexicon (2ND edition) and ACR BIRADS 2003 lexicon (4th edition) respectively.

Other similar studies (37, 47, 48) found substantial agreement. A study done by Ooms (37) using 57 mammograms reviewed by 4 experienced radiologists found substantial agreement (kappa value of 0.77, 95% CI 0.69-0.85). Redondo (47) found substantial agreement (kappa value of 0.73, 95 % CI 0.68-0.70) in a study where 21 breast radiologist reviewed 100 screening mammograms. A more recent study by Ekpo (48) where 1000 mammograms were reviewed by 5 radiologists who had recently undergone re-training in mammographic density using the ACR BI-RADS 2013 Lexicon (5th Edition) showed substantial agreement (kappa value of 0.79, 95% CI 0.78-0.83)

There was an overall significant inter-observer variability noted when rating the individual ACR breast density categories. At baseline ACR A and D had substantial agreement which declined to moderate agreement after one month. The reason for this is unclear. ACR B and C had fair and moderate agreement respectively, both at baseline and at one month interval with the greatest discordance being with ACR B. This could likely be attributed to each radiologist's variability in knowledge and perception of the breast densities. Additionally studies have shown greater variability when assessing breast densities whose categories are adjacent to each other (36, 47)

This variability is significant and of importance because breast density is an important predictor of breast cancer (1). The importance of reproducibility when reporting mammographic breast density cannot be overemphasized as it helps in decision making regarding follow up of patients found to have dense breasts due to their increased risk of breast cancer.

In this study we demonstrated substantial intra-observer agreement with kappa values ranging from 0.61(95% CI 0.48- 0.72) to 0.77 (95% CI 0.67-0.87). Similar studies done (36, 47,49) also found intraobserver variability to be substantial.

A recent study done by Ekpo (48) who used 5 readers reviewing 1000 mammograms showed near perfect agreement with kappa ranging from 0.86(95% CI 0.77-0.93) to 0.89 (95% CI 0.81-0.95) showing constancy of each reader likely attributed to the previous training done immediately prior to the study

A study by Spayne (50) found moderate to substantial intra-rater agreement. In this study radiologists reviewed 11,755 mammograms of postmenopausal women. The mammograms used were of obtained on two consecutive occasions as the breast density was not expected to change much over time. The difference in the intra-rater agreement was thus attributed to the fact that previous studies used a smaller sample size and the readers reviewed the same mammogram.

Artificial intelligence has gained traction in the assessment of mammographic breast density initially with computer aided diagnosis (CAD) and now recently with deep learning algorithms. (13). Various studies carried out by Le Boulc’h (14) and Lehman (15) found that Mammographic breast density assessment using an artificial intelligence model and a radiologist was almost similar with kappa value of 0.79 (95% CI 0.73-0.84) and 0.67(95% CI 0.66-0.68) respectively indicating substantial agreement. The increasing use of artificial intelligence in breast imaging will offer an objective and efficient way of assessing mammographic breast density among breast radiologists. It will also help reduce the variations and inconsistencies that may exist with the qualitative assessment.

Artificial intelligence is still in its early stages of implementation with minimal integration in clinical practice. It not surprising then that none of these new artificial intelligence models have been integrated into current practice in breast imaging raising concerns of their acceptability among radiologists.(13)

5.2Conclusions

This study shows a moderate level of inter- and intra- observer variability when assessing mammographic breast density but a substantial level of individual intra-observer variability highlighting the importance of training and re-training when reporting mammographic breast density

5.3 Limitations

This was a single centre study in the largest teaching and referral hospital in the country. As such generalisability of the findings may not apply to the rest of the radiologists practicing in Kenya

5.4 Recommendations

- Training and frequent retraining of the radiologists in the assessment of mammographic breast density using the ACR BI-RADS 2013 lexicon
- A longer time duration to assess the short term and long term effects of the training
- Development of quantitative assessment methods for assessment of mammographic breast density to increase reproducibility and use of deep learning models od artificial intelligence
- Global generalization of the findings can be achieved through the context of comparing it with other similar studies

FUNDING

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APPENDICES

Appendix A: Consent information document

(To be administered in English or any other appropriate language such as Kiswahili translation)

TITLE OF STUDY: **ASSESSMENT OF OBSERVER VARIABILITY IN DETERMINNG MAMMOGRAPHIC BREAST DENSITY AS PER THE AMERICAN COLLEGE OF RADIOLOGY BIRADS 2013 LEXICON.**

Principal Investigator and institutional affiliation: Dr. Githaiga Edna Wangeci, resident at University of Nairobi, Department of Diagnostic Imaging and Radiation Medicine.

There are three parts of this consent information Document.

- Introduction by the researcher
- Patient information document
- Consent certificate

Introduction:

My name is Dr. Githaiga Edna Wangeci a postgraduate student pursuing a Master's in Medicine Degree in Diagnostic Imaging and Radiation Medicine at the University of Nairobi. I am conducting the above titled study. I am requesting for your participation in this study. The aim of the consent form is to help you decide whether you would like to be included in this study or not. Kindly read through the form and feel free to ask any questions about this study. The principal investigator will be available to answer your questions at any point during the study and even thereafter.

Patient Information Document

Study Background

Breast density is a well-known and proven independent risk factor for breast cancer and can significantly affect the sensitivity of screening mammograms.

Analysis of breast density is done through the ACR- Birads lexicon 2013, which categorizes breast density into four categories (A-D) A- Almost entirely fatty, B- scattered areas of fibroglandular density, C- heterogeneously dense, which may obscure small masses and D- extremely dense, which lowers the sensitivity of mammography.

Due to the subjective nature of the visual assessment during categorization, differences may arise when assessing the breast density between two observers. It is important to assess the degree of agreement or variability as this affects the reproducibility of the report.

Study Purpose

The aim of the study was to evaluate and record the degree of inter and intra observer variability when assessing the mammographic breast density using the Breast Imaging Reporting and Data System (BIRADS), as defined by American College of Radiology.

Study Procedure

Mammograms will be selected by the principal investigator and then one will be required to review them giving each mammogram its appropriate mammographic density using the ACR-Birads 2013 lexicon. A repeat of this same procedure will be done after one month.

Role of the participant

The role of the participant is to classify each mammogram into its appropriate mammographic breast density using the ACR-Birads 2013 lexicon and then review the same mammogram again after one month as classify it again.

Benefit and risk.

Following participation in the study, the participant will be able to sharpen their skills and knowledge in the categorization of mammographic breast density using ACR-Birads lexicon

No risks are posed by taking part in the study and no additional costs will be incurred.

Confidentiality

Confidentiality will be highly observed through pseudonymization and all data obtained will be secured.

Reimbursement

No compensation, financial or otherwise, will be offered to the participants.

Voluntariness of Participation

Enrolment to participate in the study is purely voluntary and withdrawal from the study at any point is permitted with no consequence whatsoever.

Contact information.

For further clarification regarding the study please feel free to contact,

Principal researcher:

Dr. Githaiga Edna Wangeci

Radiology resident, University of Nairobi

Telephone Number: 0738254221

Email address; wangeshee@gmail.com

Supervisor:

Dr Timothy Musila Mutala,

Consultant Radiologist and Lecturer,

Department of Diagnostic Imaging and Radiation Medicine,
University of Nairobi.
Email address: mutala@uonbi.ac.ke

For queries concerning your rights as a research participant you may contact the Kenyatta National Hospital Ethics and Research Committee. It is the mandate of this committee to protect you, if you chose to participate, from harm.

KNH-UoN Ethics and Research Committee,
P.O. Box 19676-00202 OR P.O Box 20723-00202, Nairobi.
E-mail: uonknh_erc@uonbi.ac.ke
Tel number 726300-9 Ext.44102 44355.

Consent form

I, the undersigned, have read and received clear explanations of the study from the investigator and thus fully understood the information given to me regarding the above mentioned study. Any clarifications and questions I asked have been answered satisfactorily by the investigator.

I understand that my participation is voluntary and that I have not been forced to take part in the study and that I can decline without any consequence whatsover

I understand that I will not receive and neither am I entitled to any compensation or any form of remuneration for taking part in the study.

I understand that my personal information will be kept confidential.

I hereby consent to my participation in this study.
SIGNED: ………………………………… (Participant)

Date: ………………………………………………….
Unique ID: ………………………………......
SIGNED: …………………………………. (Witness)

SIGNED: ………………………………… (Patient)

Statement by the researcher

I hereby certify that I have adequately clarified the contents of the information sheet to the participant; and that the voluntary nature of their participation, confidentiality within the study; and their right to refuse or withdraw from the study without consequence is guranteed.

Name: Dr. Githiaga Edna Wangeci

Signature………………………

Date…………………………....

Appendix B: Fomu ya idhini ili kushiriki katika utafiti

Kichwa cha Utafiti: Tathmini ya tofauti za mtazamaji katika kuamua wiani za matiti kwa mammogram ukitumia mitambo ya ACR-Birads

Mpelelezi mkuu na ushirika wa kitaasisi: DR. GITHAIGA EDNA WANGECI, MWANAFUNZI WA SHAHADA YA UZAMILI KATIKA UTAMBUZI WA UGONJWA KWA MIONZI. CHUO KIKUU CHA NAIROBI, IDARA YA RADIOLOGY

Kuna njia tatu katika hii sehemu ya idhini:

- Taarifa ya mtafiti / msaidizi wa utafiti
- Karatasi ya Habari
- Cheti cha idhini

Taarifa Ya Mchunguzi

Jina langi ni Dr. Githaiga Edna Wangeci mwanafunzi wa kuhitimu akifuatilia Shahada ya Uzamili ya Tiba katika Utambuzi wa Ugonjwa kwa Mionzi katika Chuo Kikuu cha Nairobi. Nafanya utafiti na mada ni kama ilivyo elezwa hapo juu. Ningependa kuomba ushirika wako katika utafiti huu. Lengo la fomu ya idhini ni kukusaidia kuamua kama ungependa kushiriki kattika utafiti huu au la. Nakuhisi usome fomu hii na uwe na uhuru wa kuuliza swali lolote kuhusu utafiti huu. Mtafiti mkuu atakuwepo kujibu maswali yako wakati wa utafiti na hata baadaye.

Karatasi ya habari

Asili

Wiani za matiti ni jambo linalojulikana na limethibitishwa kuwa huru katika kusababisha saratani ya matiti na huathiri sana unyeti wa mammogramu.

Uchambuzi wa wiani za matiti hufanywa kutumia mtambo wa ACR-Birads ambayo huainisha wiani hizi katika makundi manne (A-D)

Hali ya kibinafsi huja kati ya waangalizi wawili kutokana na tathmini ya kuona katika kuainisha wiani hizi. Ni vyema kutathmini kiwango cha kutofautiana au makubaliano kati ya waangalizi kwa sababu uzazi wa ripoti unaadhirika.

Lengo Kuu

Madhumuni ya utafiti huu ni kuangalia tathmini ya tofauti za mtazamaji katika kuamua wiani za matiti kwa mammogram ukitumia mitambo ya ACR-Birads.

Utaratibu wa Utafiti

Picha za mammogram zitachaguliwa na mtafiti mkuu halafu wahusika watazipitia na kuzipa jamii ifaayo ya wiani ukitumia mtambo wa ACR- Birads. Utaratibu huu utarudiwa baada ya mwezi mmoja.

Jukumu la mhusika

Mhusika ataainisha kila picha ya mammogram kwa wiani ya matiti ifaayo akitumia mtambo wa ACR-Birads 2013 kisha baada ya mwezi mmoja, atazipitia hizo mammogram tena na kuziainisha tena.

Hatari na Faida

Kufuatia kushiriki kwa utafiti huu mhusika ataweza kuelewa zaidi jinsi ya kuainisha wiani ya matiti kwa Mammogram.

Hakuna hatari yoyote itampata mhusika wala hakuna gharama za ziada zitapatikana

Siri kwenye utafiti

Haki zako zitalindwa kamili na habari utakayotoa itawekwa siri wakati wote na kutumika kwa utafiti huu pekee

Fidia

Hakuna fidia, kifedha au vinginevyo itapewa kwa mshiriki

Kushiriki kwa hiari

Una uhuru wa kujiandikisha na kushiriki kwa utafiti huu na kujiondoa kutoka kushiriki wakati wowote bila matokeo yoyote.

Habari ya mawasiliano

Ikiwa unahitaji ufafanuzi zaidi kuhusu utafiti, jiskie huru kuwasiliana

Mtafiti mkuu

Dr. Githaiga Edna Wangeci

Mwanafunzi wa Uzamili utambuzi wa ugonjwa kwa mionzi

Chuo Kikuu cha Nairobi

Nambari ya simu: 0738254221

Anwani ya barua pepe: wangeshee@gmail.com

Msimamizi:

Dkt. Timothy Musila Mutala,

Mshauri wa radiolojia na Mhadhiri,

Idara ya Utambuzi wa Utambuzi na Tiba ya Mionzi,

Chuo Kikuu cha Nairobi.

Anwani ya barua pepe: mutala@uonbi.ac.ke

Kwa maswali kuhusu haki zako kama mshiriki wa utafiti unaweza kuwasiliana na Maadili na Kamati ya Maadili ya Kitaifa ya Hospitali ya Kitaifa ya Kenya. Ni jukumu la kamati hii kukulinda, ikiwa umechagua kushiriki, kutokana na madhara.

Kamati ya Maadili na Utafiti ya KNH-UoN,

P.O. Sanduku 19676-00202 AU Box Box 20723-00202, Nairobi.

Nambari ya simu; 726300-9 Ext.44102 44355.

Barua-pepe: uonknh_erc@uonbi.ac.ke

Fomu ya idhini

Mimi, niliosajiliwa, nimesoma na nikaelezwa kwa umakini kuhusu utafiti huu kutoka kwa mtafiti mkuu na nimeelewa kwa ukamilifu maelezo yote kuhusu utafiti huu. Ufafanuzi wowote na maswali yote yamejibiwa vya kuridhisha na mtafiti mkuu.

Ninaelewa kuwa ushiriki wangu ni wa hiari na kwamba na sijalazimishwa kujisajili kwa utafiti huu na kuwa ninaweza kujiondoa kutoka kushiriki wakati wowote bila matokeo yoyote.

Ninaelewa kuwa sitapokea malipo ya aina yoyote nitakaposhiriki kwa utafiti huu.

Ninaelewa kuwa habari yangu ya kibinafsi itatunzwa kwa siri.

Kwa hivyo nakubali kushiriki kwangu katika utafiti huu.

Iliyodhibitishwa: ………………………………… (mshiriki)

Tarehe: ………………………………………………….

Kitambulisho cha kipekee: …………………………… ....

Iliyodhibitishwa: …………………………………. (Shahidi)

Taarifa ya mtafiti

Kwa hivyo ninathibitisha kwamba nimeelezea kwa ukamilifu yaliyomo kwenye karatasi ya habari kwa mshiriki; kwamba wanaelewa asili ya hiari ya ushiriki wao katika masomo na usiri ambao habari zao zitatibiwa; na haki yao ya kukataa au kujiondoa kutoka kwa masomo bila matokeo yoyote imehakikishwa.

Jina: Dr. Githaiga Edna Wangeci

Sahihi………………………

Tarehe…………………………....

Appendix C: Data Collection Form

UNIQUE ID:-

GENDER

AGE:-

YEARS OF EXPERIENCE

PRIOR FELLOWSHIP IN BREAST IMAGING

ACR-Birads classification

	A	B	C	D
mammogram				
1				
2				
3				
4				
5				
6				

Appendix D- Data analysis tables

1) Inter-observer variability
2) Intra-observer Variability

Appendix E: Budget

ITEMS	QUANTITY	UNIT PRICE(KSHS)	TOTAL COST (KSHS)
Note books	4 pcs	100.00	400.00
Printing paper	3 packets	600.00	1800.00
Files	3 pcs	100.00	300.00
Cartridge	1 pc	15,000	15,000.00
Internet surfing	50 GB	120 per GB	6000.00
Writing pens	20 pcs	20	400.00
Telephone airtime			5000.00
Flash discs	2 pcs	1500	3000.00
Photocopies of data collection tool	20 copies	5.00 per page	100.00
Photocopy of final proposal	6 copies	5.00 per page(60 pages)	1800.00
Binding copies of proposal	6 copies	50.00	300.00
Ethical review fees	1	2000.00	2000.00
Miscellaneous			4,000.00
Biostatistician	1		30,000.00
Contingency (10% of total cost)			7010.00
Total			77,110.00

Appendix F: Timeline

	Sept 2020- Jan 2021	Jan 2021- April 2021	April 2021- July 2021	August 2021	Sept 2021
Proposal write up					
Submission to ERC and correction					
Data collection					
Data entry and analysis					
Report writing and dissertation submission					

Data analysis tables.

Table 1. Sociodemographic characteristics of reporting radiologists (n=)

Variable	Frequency/Median	%/IQR
Age		
Sex		
Female		
Male		
Years of experience as a radiologist		
Etc.		

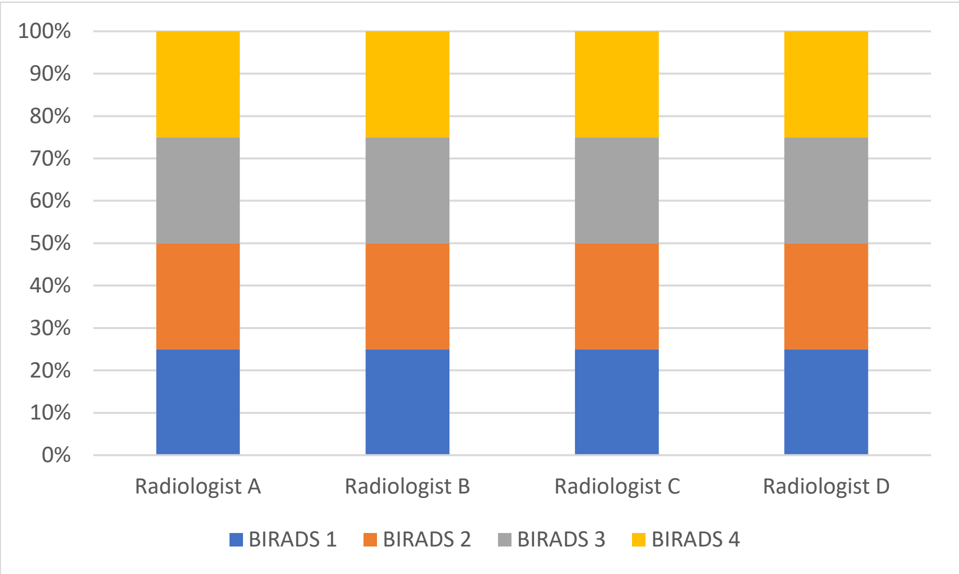

Fig.1. Percent of BIRADS breast density reported by radiologists

TABLE 1: Inter-observer agreement in breast density based on the ACR classification 5th edition between pairs of radiologists and overall agreement among all radiologists.

Pairs of observers	Weighted kappa value
A,B	
A,C	
B,C	
B,D	
C,D	
Weighted overall kappa	

(A,B,C,D)	

TABLE 2: Intra-observer agreement in breast density based on the ACR classification 5th edition between pairs of radiologists and overall agreement among all radiologists.

Radiologists	**Kappa value (95% CI)**	**P value**
A		
B		
C		
D		
Overall		

Table 3: Weighted kappa values for each BIRADS breast density category reported by the four radiologists

BIRADS breast density category	**Weighted kappa value**	**95% CI**	**P value**
1			
2			
3			
4			

Table 4: Characteristics of participants according to BIRADS breast density category

Variable	**N**	**BIRADS 1**	**BIRADS 2**	**BIRADS 3**	**BIRADS 4**	**P value**
Age (years Mean±SD						
Highest level of education attained						
Tertiary						

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7th May 2021

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.

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
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The Chair, Dept. of Diagnostic Imaging and Radiation Medicine, UoN
Supervisor: Dr. Timothy Musila Mutala, Dept. of Diagnostic Imaging and Radiation Medicine, UoN

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