Breast ultrasound in females 35 years old and below at a tertiary referral academic center in Cape Town, South Africa: indications and outcomes analysis, a retrospective quantitative study

by

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DECLARATION

I, *Nitin Juggath*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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1 List of abbreviations

SA- South Africa

BBD- Benign breast disease

GSH- Groote Schuur Hospital

PACS- Picture archiving and communications

BI-RADS- Breast imaging-reporting and data system

NHLS- National health laboratory service

N- Number

ANOVA- Analysis of variance

HREC- Human research ethics committee

ACR- American College of Radiology

NPV- Negative predictive value

Abstract

Title: Breast ultrasound in females 35 years old and below at a tertiary referral academic center in Cape Town, South Africa: indications and outcomes analysis, a retrospective quantitative study.

Background

A high number of patients are referred to our resource limited tertiary institution for specialty breast imaging. Despite the accepted application of ultrasound in young women with focal signs/symptoms, there are sparse outcomes data to validate its use in this clinical setting for certain indications and no prior study done at our facility.

Objectives

To decrease morbidity and expenditure related to breast imaging in young women by correlating clinical predictors for worrisome or benign findings, thus allowing refinement of referral criteria.

Methods

Ultrasounds performed on females below 35 years old in a 1-year period between 1st March 2019-1st March 2020 at Groote Schuur Hospital were retrospectively analyzed.
Evaluation of the reports stored on the hospitals PACS system and review of the histological diagnosis of biopsies-if performed, from the NHLS.
Clinical data and indication for referral was assessed and imaging results were categorised as either positive or negative. Positive findings were subcategorized into benign breast disease, breast abscess or malignancy.

Results

352 breast ultrasound studies were performed. 65% were palpable mass referrals, and one-third were referred without any palpable mass or focal breast pain.

67% of the studies had a positive imaging result and 33% had a negative result.
214 were classified as benign breast disease, 11 as breast abscesses and 12 were malignant.

Conclusions

Majority of disease encountered was benign breast disease. Most referrals were appropriate and predominantly for a palpable mass. One-third of studies were inappropriately referred, adding to the burden on an already strained specialty center.

CHAPTER 1: LITERATURE REVIEW

Breast Cancer

Breast cancer continues to be a universal public health dilemma and is presently the most common tumour in the world, and the leading cause of mortality due to cancer in females globally. According to GLOBOCAN, it accounts for the highest estimated number of new cancer cases in 2020, worldwide, in females of all ages amounting to 2 261 419(24.5%) cases. With a 5-year prevalence of 429 220 cases, breast cancer is the most common cancer in Africa in terms of both new cases and deaths amongst both male and females. It has an incidence rate of 40.7 per 100 000 in females. The mortality rate is similarly the highest accounting for 19.4 per 100 000. In 2020 alone, the number of new cases in females of all ages accounted for 29.5% of all cancers(1). In Zimbabwe, the incidence rate of breast cancer is 41.4 per 100 000 females from 2008-2012, second only to cervical cancer(2).
In 2016 the number of women with breast cancer in the United Kingdom had increased, accounting for 15 % of new cancer cases(3). Although a prevalent malady amongst women, breast cancer in men arises infrequently with approximately 350 cases per year in the United Kingdom.

The incidence rises with age, with women over 50 accounting for almost 80% of cancer cases. Younger women are less likely to acquire breast cancer, although the disease is more aggressive (5-year rate of survival 81% < 45 years, 86% >65 years)(3). In 2008, approximately 1.38 million new breast cancer cases were diagnosed with about 50% of all breast cancer patients and approximately 60% of mortalities occurring in resource poor developing countries(4). In developed countries such as the United States, mortality from breast cancer has significantly declined in the last few decades due to constant enhancement of screening programs, whereas developing countries are unable to implement national screening programs. Breast cancer imposes a substantial economic strain on the NHS in the UK, which is already grappling with financial challenges. The expenditure solely devoted to the breast screening initiative by NHS in England amounts to around £96 million(3).

Breast cancer is an umbrella term for several sub-types of cancers of the breast. The majority of breast cancers, ranging from 70% to 80%, are classified as ductal, while the remaining cases are attributed to various specialized subtypes such as medullary, papillary, tubular, and mucinous. The lobular subtype constitutes the remaining portion of breast cancers. (3). Breast cancer subtypes vary in their clinical manifestation, exhibit unique gene expression patterns, and possess distinct genetic and molecular properties.(5)(6).

There are multiple risk factors which predispose to the development of breast cancer, such as:

i. Sociobiological factors: Age and gender are significant risk factors for the growth of breast cancer. Seventy-five percent of new cases occurs in women aged 50 and older. There is a striking contrast between women in their fourth decade of life who are diagnosed with breast cancer at a rate of 1 in 232, compared to those in their seventh decade, who are affected at a rate of 1 in 29.

ii. Nutritional factors: High alcohol, fat, caffeine, and red meat consumption in the diet is a positive risk factor for breast cancer.

iii. Physiological factors: Medium intensity exercise reduces the risk of breast cancer, whereas obesity raises the risk of development.

iv. Genetic factors: Genetics is a small but significant risk factor, even though only 5% to 6% of cases are thought to be hereditary. BRCA-1 and BRCA-2 account for approximately 80% of hereditary breast cancers. Additionally, they have a 15% to 65% chance of acquiring ovarian cancer.

v. Family history or previous history of breast cancer: Increased risk if there is a known positive family history or previous history of breast cancer.

vi. Hormone exposure: Early menarche (<12 years old) and late menopause, never being pregnant or having first child after age 30 result in greater estrogen and progesterone subjection which increase the risk of breast cancer. Oral contraceptives and hormone replacement treatment raise the risk of breast cancer.

vii. Smoking: Tobacco use raises breast cancer risk since it includes chemical agents that cause cancer. (7)(8).

Breast Cancer in South Africa.

Most recent available national estimates regarding the frequency of breast cancer diagnosis in South African females indicates a 1 in 25 life time risk of developing breast cancer and accounting for the highest percentage (over 23%) of cancers in females in South Africa (SA) (9). The incidence of breast cancer in SA varies by age and place, but there is evidence that it is becoming more common(10). In the Western Cape Province, breast cancer is relatively common, accounting for 3% of all deaths in adult women in Cape Town- the highest percentage for any other cancer(11). In the Eastern Cape Province, breast cancer had an incidence rate of 12.7 cases per 100 000 females between 2008-2012, only ranking below oesophageal (14.6 cases per 100 000) and cervical cancer (30 cases per 100 000)(2).
Some of the general risk factors associated with breast cancer development (as mentioned previously) have been investigated specifically in African females;

- The gynaecologic and reproductive characteristics observed among African populations generally lead to a reduced frequency of ovulatory cycles throughout their lives, consequently leading to a decline in the risk of developing breast cancer. Various trends that have been observed include delayed menarche, having multiple births, starting childbearing at a young age, and breastfeeding for extended periods. All of these characteristics result in decreased levels of endogenous estrogen throughout one's lifetime(10).

- Rosenberg et al. conducted an assessment on the link between breast cancer risk and childbirth among South African women, revealing comparable patterns to those observed in western populations. In their study, women of mixed ethnic backgrounds who gave birth to their first child at the age of 30 years or above experienced a twofold rise in breast cancer risk compared to those who had their first child at 16 years of age or below(12).

- A typical dietary regimen in Africa primarily comprises grains, vegetables, and fiber, with minimal amounts of fat and protein. It is worth noting that this particular pattern of nutritional intake may offer a protective effect against the risk of developing breast cancer(13).
- A particular study conducted in South Africa has revealed that the incidence rates of breast cancer in urban areas are twice as high as those in rural areas. Urban areas are often associated with adopting westernized behaviors and lifestyles. Additionally, urban areas tend to house more affluent women, and thus, the variations in incidence rates can be partially attributed to differences in factors such as the age of menarche, the number of pregnancies, the age at which the first child is born, and the age at which menopause occurs(14).

Breast cancer is associated with a high mortality rate in SA due to limited public health awareness, knowledge of breast cancer risk factors and the restricted access to the few available specialty breast clinics and oncology care facilities(15)(16)(10). A study conducted in South Africa involving 2033 patients, both black and white, revealed that black Africans experienced delays in seeking medical attention. This delay consequently led to the development of larger tumours and more advanced nodal pathology compared to their white South African counterparts(17).

Another important contributing factor to the high mortality rate in SA is the absence of a breast cancer screening program and the majority of cancers are diagnosed symptomatically and at an advanced stage of disease(18).

Breast cancer in Young Females

The majority of breast cancer is found in postmenopausal women, and about 75 % of cases are diagnosed in women over the ages of 50. Even though it is an uncommon disease in young women affecting approximately 4-6% of women under the age of 40, current statistics indicate a rise in the incidence(19). The increased incidence of breast cancer in young patients may be connected to changes in diet, hormone exposure and advanced age of first pregnancy. Family history of breast cancer possibly related to a familial syndrome may also be responsible for the disease in younger patients, although most of these cases appear to be sporadic(20).
In women under 40 years of age, breast cancer may present more aggressively and have a worse prognosis(21). Delayed diagnosis contributes to the worse prognosis and is often due to lack of education about breast cancer and consequent delay in seeking medical care, no screening programs in this age group, fast tumour growth and dense pattern of breast parenchyma, which may impair clinical and imaging detection of tumours.(20)

Benign Breast Disease

Benign breast diseases (BBD) include all non-malignant conditions of the breast and is a broad category of pathologic diagnosis including, but not limited to fibroadenomas , cysts, fibrocystic disease, papillomas, and ductal epithelial proliferations , with or without atypia. Although most BBDs are not associated with an increased risk of breast cancer, studies have demonstrated a 4-5 fold increased risk in BBD with atypia and a 1.5-2 fold in BBDs without atypia of developing breast cancer(22). Frequently encountered worries encompass a self-detected palpable lump, skin changes, breast pain, or nipple discharge. Certain benign conditions can be readily distinguished using conventional imaging methods, while others may necessitate more advanced imaging techniques or a biopsy to establish an accurate diagnosis(22). When dealing with benign breast lesions, a key consideration is to assess if the pathology results of the biopsy align with the findings from the examination and imaging, known as clinical- or radiologic-pathologic concordance. In cases where these findings do not align, it is generally recommended to surgically remove the lesions(23). Clinical management is contingent upon patient-specific factors as well as individual risk factors linked to the lesion. Certain lesions necessitate no further intervention, thereby allowing for the resumption of routine screening. Benign breast changes occur more frequently among women in their child-bearing years, reaching their highest occurrence between the ages of 30 and 50. Conversely, the highest incidence of breast cancer is observed during the postmenopausal stage(24). Hindrance in evaluating the epidemiology of BBDs include the lack of universal acceptance of a standardized histological classification system for BBDs and the lack of true prevalence statistics in the general population(23). Collective incidence of biopsy-proven BBDs is approximately 10-20% and in autopsy studies reveal a much higher incidence of approximately 50%(23).

Breast Pain

Breast pain, also known as mastalgia, is common and is experienced in up to 70-80% of women during their lifetime(24)(25). Although common, it is suspected to be under reported and under-studied even though it is a leading symptom for which women seek medical attention. Hormonal influences are responsible for cyclical breast pain. Non-cyclical breast pain is not related to the menstrual cycle and can be idiopathic and related to a multitude of causes such as pregnancy, perimenopause, musculoskeletal abnormalities, chronic pain syndromes, ill-fitting brassiere, infections and post-surgical causes(26). Breast pain is not a common presentation for solid masses in the breast, however, it may be frequently associated with cysts or fibroadenomas. Isolated breast pain is associated with cancer in less than 1% of cases(27). Imaging of mastalgia is related to the suspected etiology. Inappropriate imaging for breast pain results in significant usage of health care resources. Cyclical breast pain does not require an imaging work-up. Focal, non-cyclical breast pain investigations include ultrasound for women aged younger than 40 years, and mammography and ultrasound for women aged 40 years and older(28). Most breast pain resolves spontaneously, and management is often supportive. If pain breast pain persists, imaging and management should follow a stepwise approach.

Breast Imaging in women under 35 years old.

In a study performed by Harris et al to determine appropriate indications for breast imaging in 625 women below 35 years old, the study revealed the only important indications were a palpable mass and suspicion of an abscess. All other indications were associated with a very low prevalence of any imaging abnormality(29). According to the American College of Radiology imaging options in the context of a palpable mass and/or clinically significant breast pain (focal and non-cyclical), include diagnostic mammography, digital breast tomosynthesis(DBT) and targeted-breast ultrasound and are dependent on patient age and degree of radiologic suspicion(30)(28). More advanced imaging technologies such as MRI, positron emission mammography or molecular breast imaging do not feature as initial imaging modalities in the context of a palpable breast lump or significant breast pain.

Due to the possible increased radiation risk for mammography and the low incidence of breast cancer in younger women, the recommended imaging evaluation protocol for women younger than 30 years old differs from that carried out in older women, where mammography and DBT are recommended. Ultrasound is recommended as the first line investigation for women younger than age 30 years(30). Furthermore, younger women usually have more dense breast tissue which is associated with lower sensitivity to mammography(31). However, mammography or DBT can be performed as a complementary investigation in younger women to further characterize and assess for malignant features that may be seen on these imaging modalities alone. Mammography, DBT or ultrasound can be used as the initial investigation for women aged 30-39 years with indications for imaging according to the American College of Radiology(30).

References

1. International Agency for Research on Cancer WHO. Africa Cancer Fact sheets. Globocan [Internet]. 2021;598:1–2. Available from: https://gco.iarc.fr/today/data/factsheets/populations/903-africa-fact-sheets.pdf
2. International Agency for Research on Cancer. Cancer incidence in five continents, vol. XI. Vol. 11, European Journal of Cancer. 2017. 127–129 p.
3. Chopra S, Davies EL. Breast cancer. Med (United Kingdom) [Internet]. 2020;48(2):113–8. Available from: https://doi.org/10.1016/j.mpmed.2019.11.009
4. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol. 2008;9(8):730–56.
5. Perou CM, Sørile T, Eisen MB, Van De Rijn M, Jeffrey SS, Ress CA, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747–52.
6. Curtis C, Shah SP, Chin SF, Turashvili G, Rueda OM, Dunning MJ, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature. 2012;486(7403):346–52.
7. Angahar LT. An Overview of Breast Cancer Epidemiology, Risk Factors, Pathophysiology, and Cancer Risks Reduction. MOJ Biol Med. 2017;1(4):92–6.
8. Reynolds P. Smoking and breast cancer. J Mammary Gland Biol Neoplasia. 2013;18(1):15–23.
9. South African National Cancer Registry. Cancer in South Africa (2017). WwwNcrAcZa [Internet]. 2017;1. Available from: http://www.cansa.org.za/south-african-cancer-statistics/
10. Fregene A, Lisa A, Newman MPH, Newman LA. Breast Cancer in Sub-Saharan Africa: How Does It Relate to Breast Cancer in African-American Women? 2005; Available from: www.interscience.wiley.com
11. Groenewald P, Bradshaw D, Daniels J, Matzopoulos R, Bourne D, Blease D, et al. Cause of death and premature mortality in Suggested citation Acknowledgements Copies of the report [Internet]. 2001. 2001–

2006 p. Available from: www.mrc.ac.za/bod.bod.htm%5Cnwww.capetown.gov.za/health%5Cnwww.capegateway.gov.za/health

12. Bedoya AM, Arcila AL, Cardona-Arias JA. Risk factors for breast cancer. Rev Cuba Obstet y Ginecol. 2019;45(2).
13. Djuric Z, Depper JB, Uhley V, Smith D, Lababidi S, Martino S, et al. Oxidative DNA damage levels in blood from women at high risk for breast cancer are associated with dietary intakes of meats, vegetables, and fruits. Vol. 98, Journal of the American Dietetic Association. 1998. p. 524–8.
14. Hoffman M, de Pinho H, Cooper D, Sayed R, Dent DM, Gudgeon A, et al. Breast cancer incidence and determinants of cancer stage in the Western Cape. S Afr J Obstet Gynaecol. 2001;7(1).
15. Breast cancer awareness | Western Cape Government [Internet]. [cited 2021 Jul 31]. Available from: https://www.westerncape.gov.za/general-publication/breast-cancer-awareness
16. Schoeman M, Apffelstaedt JP, Baatjes K, Urban M. Implementation of a breast cancer genetic service in South Africa - Lessons learned. South African Med J. 2013;103(8):529–33.
17. Dansey RD, Hessel PA, Browde S, Lange M, Derman D, Nissenbaum M, et al. Lack of a significant independent effect of race on survival in breast cancer. Cancer. 1988;61(9).
18. Moodley J, Constant D, Mwaka AD, Scott SE, Walter FM. Mapping awareness of breast and cervical cancer risk factors, symptoms and lay beliefs in Uganda and South Africa. PLoS One [Internet]. 2020;15(10 October):1–17. Available from: http://dx.doi.org/10.1371/journal.pone.0240788
19. Radecka B, Litwiniuk M. Breast cancer in young women. Ginekol Pol. 2016;87(9):659–63.
20. Eugênio DSG, Souza JA, Chojniak R, Bitencourt AGV, Graziano L, Souza EF. Breast cancer features in women under the age of 40 years. Rev Assoc Med Bras. 2016;62(8):755–61.
21. Emiroglu M, Karaali C, Sert I, Salimoglu S, Ugurlu L, Aksoy S, et al. Comparison of Clinical and Pathological Differences of Breast Cancer

Patients under 35 and above 55 Years of Age. J Breast Heal. 2015;11(3):123–7.

22. Silvera SAN, Rohan TE. Benign proliferative epithelial disorders of the breast: A review of the epidemiologic evidence. Breast Cancer Res Treat. 2008;110(3):397–409.
23. Friedenreich CM, Bryant HE, Alexander F, Hugh J, Danyluk J, Page DL. Risk factors for benign proliferative breast disease. Int J Epidemiol. 2000;29(4):637–44.
24. Mastalgia: a review of management. [Internet]. [cited 2021 Aug 25]. Available from: https://reference.medscape.com/medline/abstract/16444894
25. Griffith CDM, Dowle CS, Hinton CP, Blarney RW. The breast pain clinic: A rational approach to classification and treatment of breast pain. Postgrad Med J. 1987;63(741):547–9.
26. Sivarajah R, Welkie J, Mack J, Casas RS, Paulishak M, Chetlen AL. A review of breast pain: Causes, imaging recommendations, and treatment. J Breast Imaging. 2020;2(1):101–11.
27. Mohallem Fonseca M, Lamb LR, Verma R, Ogunkinle O, Seely JM. Breast pain and cancer: should we continue to work-up isolated breast pain? Breast Cancer Res Treat [Internet]. 2019;177(3):619–27. Available from: https://doi.org/10.1007/s10549-019-05354-1
28. Holbrook AI, Moy L, Akin EA, Baron P, Didwania AD, Heller SL, et al. ACR Appropriateness Criteria ® Breast Pain. J Am Coll Radiol [Internet]. 2018;15(11):S276–82. Available from: https://doi.org/10.1016/j.jacr.2018.09.014
29. Harris V, Jackson V. Indications for Breast Imaging in Women under Age 35 Years. RSNA. 1989;445–8.
30. Moy L, Heller SL, Bailey L, D'Orsi C, DiFlorio RM, Green ED, et al. ACR Appropriateness Criteria® Palpable Breast Masses. J Am Coll Radiol [Internet]. 2017;14(5):S203–24. Available from: http://dx.doi.org/10.1016/j.jacr.2017.02.033
31. Carney PA, Miglioretti DL, Yankaskas BC, Kerlikowske K, Rosenberg R, Rutter CM. Erratum: Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of

screening mammography (Annals of Internal Medicine (2003) 138 (168-175)). Ann Intern Med. 2003;138(9):771.

32. WESTERN CAPE [Internet]. [cited 2021 Jul 31]. Available from: https://apps.statssa.gov.za/census01/Census96/HTML/press/Part017.html

33. Harvey JA, Mahoney MC, Newell MS, Bailey L, Barke LD, Orsi CD, et al. ACR Appropriateness Criteria Palpable Breast Masses. JACR [Internet]. 2013;10(10):742-749.e3. Available from: http://dx.doi.org/10.1016/j.jacr.2013.06.013

34. Gundry KR. Breast ultrasound: Indications and findings. Clin Obstet Gynecol. 2016;59(2):380–93.

35. Loving VA, DeMartini WB, Eby PR, Gutierrez RL, Peacock S, Lehman CD. Targeted ultrasound in women younger than 30 years with focal breast signs or symptoms: Outcomes analyses and management implications. Am J Roentgenol. 2010;195(6):1472–7.

36. Fraker JL, Clune CG, Sahni SK, Yaganti A, Vegunta S. Prevalence , Impact , and Diagnostic Challenges of Benign Breast Disease : A Narrative Review. 2023;(May):765–78.

37. Orr B, Kelley JL. Benign Breast Diseases: Evaluation and Management. Clin Obstet Gynecol. 2016;59(4).

38. Bartow SA, Pathak DR, Black WC, Key CR, Teaf SR. Prevalence of benign, atypical, and malignant breast lesions in populations at different risk for breast cancer. A forensic autopsy study. Cancer. 1987;60(11):2751–60.

39. Cole P, Elwood JM, Kaplan SD. Incidence rates and risk factors of benign breast neoplasms. Am J Epidemiol. 1978;108(2).

40. Park YM, Kim EK, Lee JH, Ryu JH, Han SS, Choi SJ, et al. Palpable breast masses with probably benign morphology at sonography: Can biopsy be deferred? Acta radiol. 2008;49(10).

41. Raza S, Chikarmane SA, Neilsen SS, Zorn LM, Birdwell RL. BI-RADS 3, 4, and 5 lesions: Value of US in management - Follow-up and outcome. Radiology. 2008;248(3).

42. Graf O, Helbich TH, Fuchsjaeger MH, Hopf G, Morgun M, Graf C, et al. Follow-up of palpable circumscribed noncalcified solid breast masses at

mammography and US: can biopsy be averted? Radiology. 2004;233(3):850–6.

43. Graf O, Helbich TH, Hopf G, Graf C, Sickles EA. at US : Is Follow-up an Acceptable Alternative to Biopsy ? 1 Methods : Results : Conclusion : Radiology. 2007;244(1).

44. Harvey JA, Nicholson BT, LoRusso AP, Cohen MA, Bovbjerg VE. Short-term follow-up of palpable breast lesions with benign imaging features: Evaluation of 375 lesions in 320 women. Am J Roentgenol. 2009;193(6):1723–30.

CHAPTER 2: FULL TEXT JOURNAL ARTICLE FOR SUBMISSION

2 Abstract

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A high number of patients are referred to our resource limited tertiary institution for specialty breast imaging. Despite the accepted application of ultrasound in young women with focal signs/symptoms, there are sparse outcomes data to validate its use in this clinical setting for certain indications and no prior study done at our facility.

Objectives

To decrease morbidity and expenditure related to breast imaging in young women by correlating clinical predictors for worrisome or benign findings, thus allowing refinement of referral criteria.

Methods

Ultrasounds performed on females below 35 years old in a 1-year period between 1st March 2019-1st March 2020 at Groote Schuur Hospital were retrospectively analyzed.
Evaluation of the reports stored on the hospitals PACS system and review of the histological diagnosis of biopsies-if performed, from the NHLS.
Clinical data and indication for referral was assessed and imaging results were categorised as either positive or negative. Positive findings were subcategorized into benign breast disease, breast abscess or malignancy.

Results

352 breast ultrasound studies were performed. 65%(229) were palpable mass referrals, and one-third were referred without any palpable mass or focal breast pain.
67% of the studies had a positive imaging result and 33% had a negative result.
214 were classified as benign breast disease, 11 as breast abscesses and 12 were malignant.

Conclusions

Majority of disease encountered was benign breast disease. Most referrals were appropriate and predominantly for a palpable mass. One-third of studies were inappropriately referred, adding to the burden on an already strained specialty center.

Keywords:
Benign breast disease, breast abscess, malignancy, palpable mass, focal breast pain.

Introduction

Breast disease stands as a formidable global health challenge, affecting millions of individuals worldwide and demanding concerted efforts in research, prevention, and treatment. Breast cancer, in particular, is a pervasive concern, representing the most commonly diagnosed cancer among women globally and accounting for the highest estimated number of new cancer cases worldwide in 2020. In Africa, it is the most common cancer in terms of new cases and deaths amongst males and females(1).

In the context of breast imaging for young females, particularly those below 30 years old, breast ultrasound emerges as a pivotal diagnostic tool. This is underscored by findings from a study conducted by Harris et al, which demonstrated that, among women in this age group, indications such as a palpable mass and suspicion of an abscess were the only factors significantly associated with imaging abnormalities(29). Given the concerns surrounding radiation exposure in younger women and the lower incidence of breast cancer in this demographic, the American College of Radiology recommends ultrasound as the first-line investigation for those under 30(28)(30). This preference is further justified by the higher density of breast tissue in younger individuals, which diminishes the sensitivity of mammography. While mammography and digital breast tomosynthesis (DBT) remain important complementary tools, ultrasound stands out as a crucial and non-invasive initial imaging modality for the comprehensive evaluation of breast health in young females, ensuring a balanced consideration of both diagnostic accuracy and patient safety.

Have the referrals for specialist breast imaging in young females to our resource limited tertiary institute been appropriate or not, despite the widely accepted application of ultrasound in young women with focal signs or symptoms?

There has been a noticeable rise in the number of younger women being referred for breast ultrasounds, even though the incidence and prevalence of cancer is exceedingly uncommon among this demographic.

Our study aimed to decrease morbidity and expenditure of resources related to breast imaging in women below 35 years old by correlating clinical predictors for worrisome or benign imaging findings on ultrasound, thus, allowing refinement of referral criteria and imaging protocols.

Research methods and design

Study design

Our study is a retrospective, quantitative study to evaluate the imaging findings of breast ultrasounds performed in women below 35 years old at Groote Schuur Hospital (GSH) and correlating these findings with their clinical symptoms and diagnosis.

Setting

Groote Schuur Hospital is a tertiary academic hospital hosting two distinct breast clinics that refer patients to the radiology department for ultrasounds and mammograms. Annually, these clinics collectively process between 4500 to 5500 new patients exhibiting breast-related symptoms.
Our institute is one of three specialty referral pathways managing breast disease in the Western Cape public sector catering for approximately two million females (15)(32).

Study population and sampling strategy

Inclusion criteria:

- Females <35 years old that underwent a breast ultrasound in a 1-year period between 1st March 2019-1st March 2020.

Exclusion criteria:

- Females 35 years old and above.
- Males and transgender population.

Sample size criteria was based on a one-way ANOVA comparing three groups, with medium effect size (Cohen's $f = 0.25$), the suggested sample size is n(number) = 252. In addition, previous studies investigating a similar topic have sample sizes generally ranging from 206-257 (20). As such, the target minimum number of patients for this study will be 250 patients.

Ultrasound images and reports stored in the Picture Archiving and Communications (PACS) database system were reviewed.

Detailed search was performed, using query builder (Philips, xiris 8.3.16) database search tool to access all ultrasound studies on the PACS system for the period 1st March 2019 to 1st March 2020. The search results were filtered by making use of the search parameters: “ultrasound: breast” and “age: <35”.

Data collection and analysis

The following data fields were captured from patient referral forms and imaging reports:

- Patient age
- Indication for referral
- Imaging results

Histological diagnosis for findings that were biopsied were captured from the National Health Laboratory Service (NHLS).

Descriptive data was reported as means and standard deviations for continuous variables, and proportions for categorical variables. Data analysis was conducted using SPSS Version 27, with the threshold for statistical significance set of $p = 0.05$. Demographic and clinical data was compared between our three positive finding groups (benign disease, breast abscess or malignant). One-way ANOVA’s compared continuous outcome variables between the three groups. Chi-square analyses tested the associations between categorical outcome variables and the three groups.

Ethical Considerations

This retrospective study was approved by the local institutional review board and Human Research Ethics Committee (HREC).
HREC REF: 333/2022

Results

A total of 352 breast ultrasound studies were evaluated, of which 237 had a positive imaging finding and 115 were negative.

Of the studies with positive imaging findings, 214 were BBD, 11 breast abscess and 12 malignancies (Table 1).

229 patients were referred for a palpable mass, 4 for focal breast pain and 114 patients were referred for reasons other than a palpable mass or focal breast pain (Table 1).

Of the 233 referrals for a palpable mass or focal breast pain, 193 had positive imaging findings and 40 were negative. 11 of these were malignancy, 8 breast abscess and 174 BBD.

Of the 114 patients that were referred for other reasons, 73 had negative imaging and 41 had positive imaging findings; 37 BBD, 3 breast abscesses and 1 malignancy (Table 2).

5 patients included in the study did not have a documented referral indication.

Of the 214 patients diagnosed with BBD by imaging, 173 were referred for a palpable mass, 1 for focal breast pain, 37 for other reasons and 3 did not have documented indications.
Of the 12 patients diagnosed with a malignancy by imaging, 11 were referred for a palpable mass and 1 for other reasons.
Of the 11 patients diagnosed with a breast abscess by imaging, 7 were referred for a palpable mass, 1 for focal breast pain and 3 for other reasons (Table 3).

A biopsy was performed in 143 of the studies, diagnosing BBD in 113 cases, breast abscess in 9 and malignancy in 13 (Table 3).

2 patients referred with palpable masses had negative imaging, however a biopsy diagnosed benign breast disease.

1 patient referred with a palpable mass had negative imaging, however a biopsy diagnosed a malignancy.

Regarding the age of this cohort, the median age was 28 and the interquartile range was 8 with no outliers (Table 4).

The interquartile range of age in patients with BBD, the median age was 27 with no outliers.

The interquartile range of age in patients with breast abscess, the median age was 30 with a single outlier aged 18.

The interquartile range of age in patients with malignancy, the median age was 32 with no outliers (Table 5).

The average age of malignancy was 32 years old. The youngest 28 years and oldest 34 years old.

Table 1 : Indications, Imaging and Biopsy Results

Total Number of Studies	**n = 352**
Positive Imaging	237 (67%)
Negative Imaging	115 (33%)
Positive Findings	**n = 237**
Benign Breast Disease	214 (90%)
Breast Abscess	11 (5%)
Malignancy	12 (5%)
Indication for Referral	**n = 352**
Palpable Mass	229 (65%)
Focal Breast Pain	4 (1%)
*Other	114 (32%)
N/A	5 (1%)
Biopsy Performed	
Yes	143 (41%)
No	209 (59%)

*Other: any indication other than a palpable mass or focal breast pain

N/A: not applicable

Table 2: Referral Indication vs Imaging Findings

Referral Indication	Total Number	Positive Imaging	Negative Imaging	BBD	Breast Abscess	Malignancy
Palpable Mass or Focal Breast Pain	233	193 (83%)	40 (17%)	174	8	12
*Other	114	41 (36%)	73 (64%)	37	3	1
N/A	5	3 (60%)	2 (4%)	3	0	0
*Other: any indication other than a palpable mass or focal breast pain N/A: not applicable						

Table 3: Clinical indicators between Benign breast disease, Breast abscess and Malignancy

	Benign Breast Disease	Breast Abscess	Malignancy	Test Statistics		
	n = 214	n = 11	n = 12	χ^2	*p*	*V*
Referral Indication				Fischer's	.109	0.218
Palpable Mass	175 (82%)	7 (64%)	12 (100%)			
Focal Breast	1 (0.5%)	1 (9%)				
*Other	37 (17%)	3 (27%)	0 (0%)			
N/A	3 (1%)					
Imaging Result				Fischer's	.468	0.086
Negative	2 (1%)	0	1 (8%)			
Positive	212 (99%)	11 (100%)	11 (92%)			
Biopsy Diagnosis				14.00	.001	0.024
No	103 (48%)	2 (18%)	0			
Yes	111 (52%)	9 (82%)	12 (100%)			
	Benign Breast Disease	**Breast Abscess**	**Malignancy**	***F***	***p***	***Eta²***
Average Age	26	28	32	7.50	<.001	0.06
***Other: Any indication other than a palpable mass or focal breast pain**						

Table 4: Age interquartile range

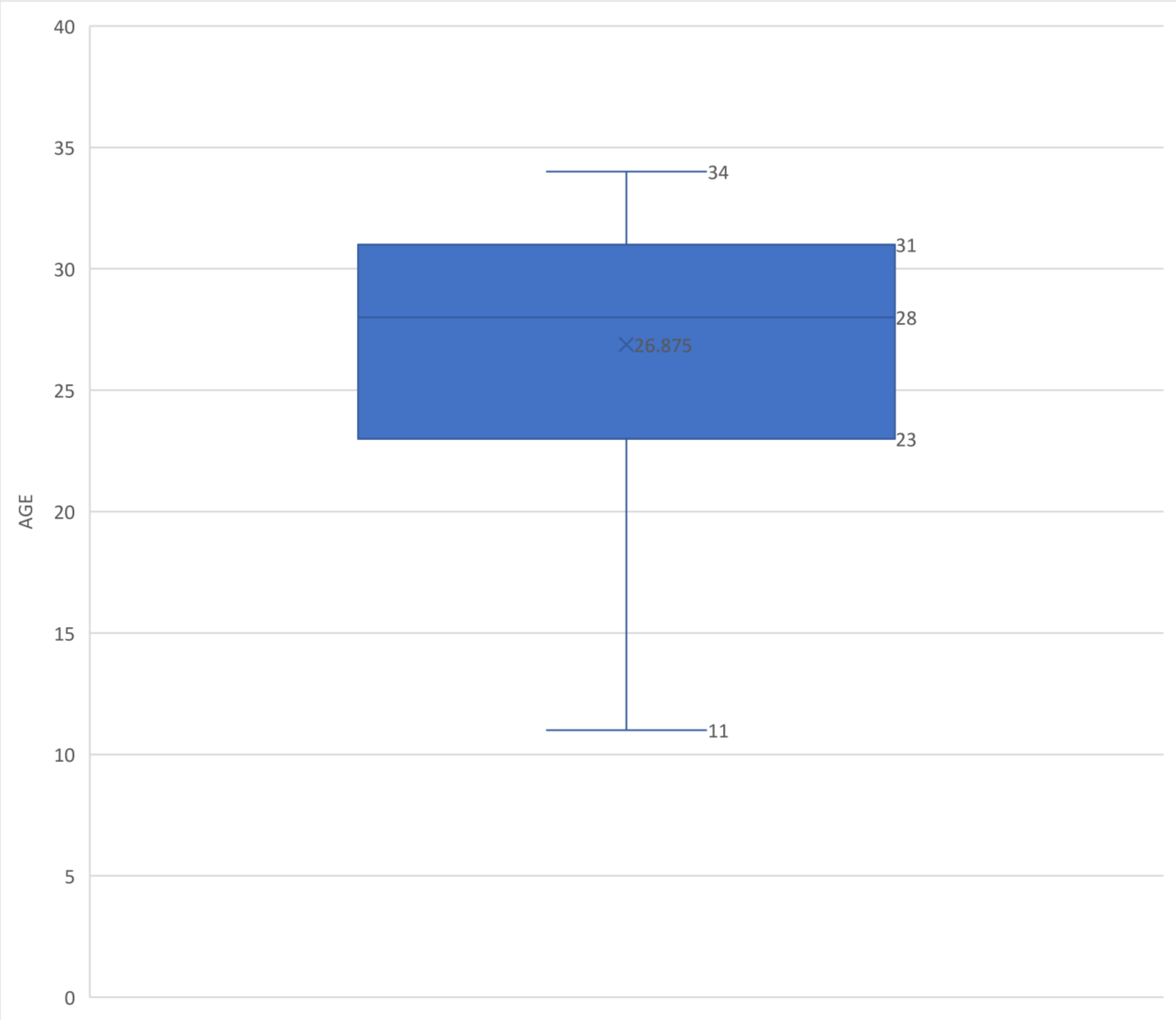
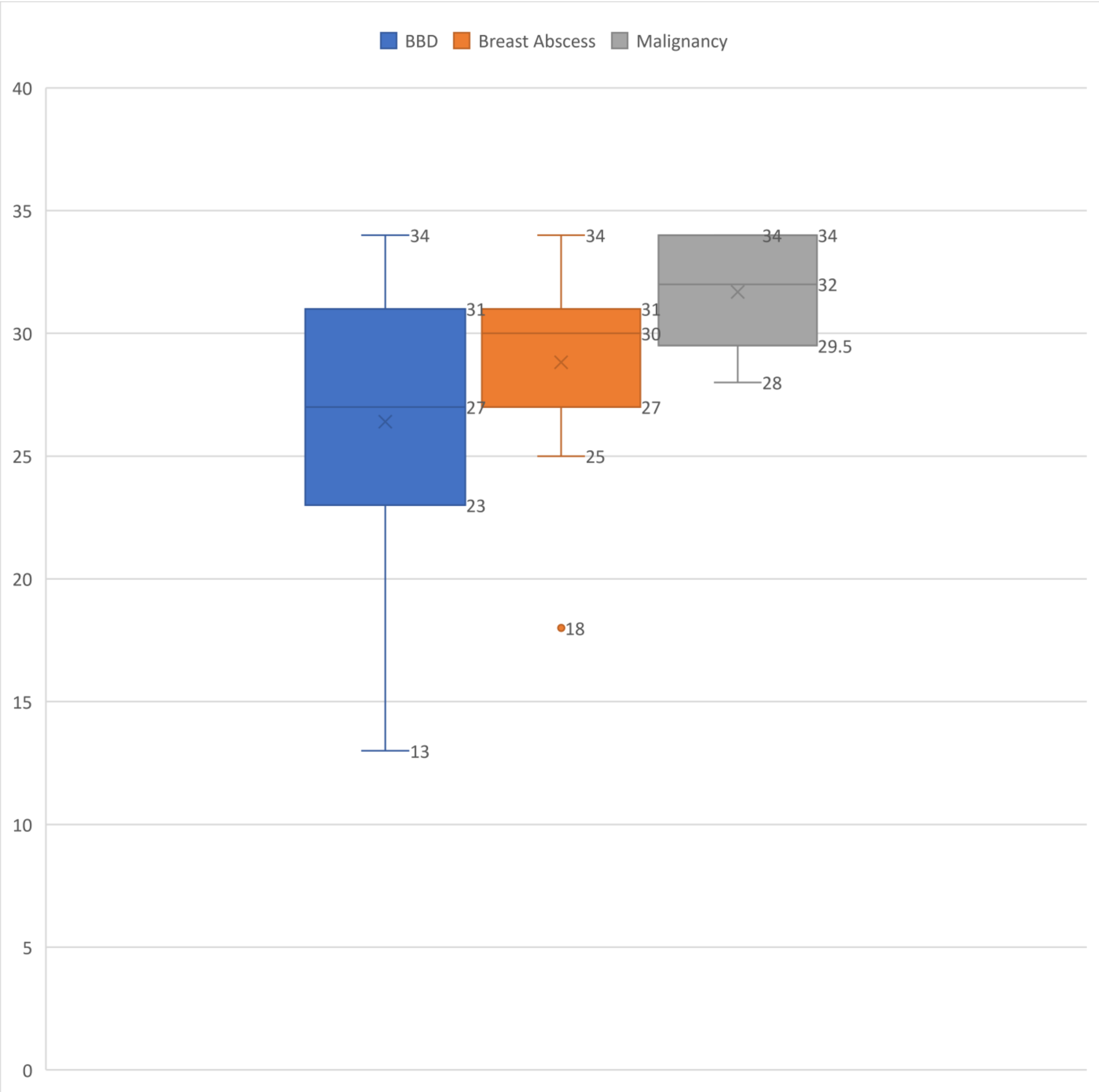


Table 5: Interquartile range of age and positive findings



Discussion

The data suggests that one-third of the referrals we received were inappropriate according to American College of Radiology (ACR) appropriateness criteria(33), and the overwhelming majority of positive imaging findings were BBD (214/90%).

The incidence of breast cancer in our study was 3 %(12) from the 352 cases evaluated in women 35 years old and below, with an average age of 32 years. This is comparable to other studies demonstrating an incidence of approximately 4-6% under the age of 40(19), and even less under 30 years approaching <1%(34). Breast cancer is predominantly found in postmenopausal women and the incidence rises with age. It accounts for the highest percentage (over 23%) of cancers in females in South Africa(9). Younger women are less likely to acquire breast cancer, although the disease is more aggressive(3). A similar study had a 0.4% incidence rate of breast malignancy, however evaluating a younger population group below the age of 30 years old(35). Our study would demonstrate a reduced incidence of breast malignancy in this age group of 1% as the majority with malignancy were over the age of 30. In our study, a palpable mass was the most important clinical indicator for malignancy being present in all 12 cases with positive imaging findings.

During the one-year study period we performed a total of 352 ultrasounds. 233/66% of these studies were appropriate referrals for either a palpable mass or focal breast pain, however 114/32% were inappropriate referrals. According to the ACR appropriateness criteria for imaging, a palpable mass or focal, non-cyclical breast pain below the age of 40 warrants imaging(28,33). In our study 73/64% of the inappropriate referrals were normal, and of these cases with positive findings 37/90% were BBD and just 1/2% malignancy was discovered-an incidence of 0.9 % which was much lower compared to the study performed by Harris et al. of 5%. This lower incidence may be due to the smaller sample size in our study, approximately half that in comparison.

BBD accounted for 214/90% of the positive image findings in our study which aligns with the anticipated outcomes established from the outset of this study. Although widely demonstrated that benign breast disease is prevalent amongst younger women, particularly in their child-bearing ages, the exact incidence is difficult to quantify due to the lack of true prevalence statistics in the general population, as many of these cases are not biopsy proven as surveillance is preferred(36,37). Based on autopsy studies carried out in a study by Bartow et al., the prevalence of BBD is estimated to be about 50% amongst woman during their lifetime, whereas the cumulative incidence of biopsy-proven BBD is only 10-20% as estimated from epidemiological studies(38,39). Surveillance has the benefit of lower morbidity compared to biopsy, as concluded by previous studies(40–44). The reduced cost associated with surveillance as opposed to biopsy was further underlined by Harvey et al. Approximately half (113/52%) of BBD were proven by biopsy in our study suggesting a lower threshold for performing biopsy in our setting at the expense of increased costs. Factors such as patient preference and low-income population group restricting access to specialty breast clinics are thought to play a role(10,15,16). Of note, 3 out of 115(2.6%) cases in our study with a palpable mass had false-negative imaging but a biopsy proven breast disease, 2 BBD and 1 malignancy. A negative predictive value of 97.3%, just below the NPV from prior studies of 98-100%(41).

There are limitations in this study. It is a retrospective study over a 1 year period in a resource limited tertiary institute. Ultrasounds were performed by general radiologists and registrars in training, albeit in a centre offering specialised breast imaging.

The study's implications for clinical practice are noteworthy. The observed discrepancy between referral patterns and outcomes, particularly the high rate of BBD and the rarity of malignancy, emphasizes the need for more refined and evidence-based referral criteria. The data suggests that guidelines and protocols should focus on prioritizing referrals for palpable masses and focal breast pain with a higher likelihood of meaningful findings, while being cautious about unnecessary imaging.

This study opens several avenues for future research that can further contribute to our understanding of breast imaging in young women and guide clinical practices in our setting.
A prospective study to implement clinical decision referral protocols. Assess how these protocols influence referring physician behaviour and the appropriateness of referrals, potentially leading to improved patient outcomes and more efficient resource utilization.
Other prospective studies directed at improving patient education about breast disease symptoms and evaluate the impact it has on health care could also be explored.

Conclusion

The results of the study shed light on several key aspects. Notably, the study population exhibited a high number (352) of referrals in a 1 year period, indicating the growing prominence of breast ultrasounds in younger women despite the low incidence of worrisome findings, particularly breast cancer, in this age group. The analysis of indications for referral revealed that approximately one-third of the referrals were potentially inappropriate based on established appropriateness criteria.

The imaging findings underscored the dominance of benign breast disease (BBD) as the predominant outcome, accounting for most of the positive imaging results. This finding aligns with expectations, given the known prevalence of benign breast conditions in younger women. The study also highlighted that a minute amount of cases exhibited malignancy, emphasizing the rarity of breast cancer in this demographic.

This study contributes valuable insights into the utilization and outcomes of breast ultrasounds in young women, emphasizing the need for targeted approaches to clinical management and resource allocation. By refining referral criteria and imaging protocols, healthcare providers can strive to optimize patient care, reduce unnecessary interventions, and allocate resources more efficiently, ultimately improving the well-being of the patient population.

This study opens several avenues for future research that can further contribute to our understanding of breast imaging in young women and guide clinical practices in our setting.
A prospective study to implement clinical decision referral protocols. Assess how these protocols influence referring physician behaviour and the appropriateness of referrals, potentially leading to improved patient outcomes and more efficient resource utilization.
Other prospective studies directed at improving patient education about breast disease symptoms and evaluate the impact it has on health care could also be explored.

Acknowledgments
The authors acknowledge Dr M. Henry who conducted the statistical analysis.

Competing interests
The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

Authors contribution
N. Juggath was the lead author, gathered the data and prepared the manuscript and R. Gamieldien supervised the project, edited and approved the final manuscript for submission.

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No external funding was received for conducting of this research.

Data availability
Data is available from the authors upon reasonable request.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect official policy or that of our institution.

References

1. International Agency for Research on Cancer WHO. Africa Cancer Fact sheets. Globocan [Internet]. 2021;598:1–2. Available from: https://gco.iarc.fr/today/data/factsheets/populations/903-africa-fact-sheets.pdf
2. International Agency for Research on Cancer. Cancer incidence in five continents, vol. XI. Vol. 11, European Journal of Cancer. 2017. 127–129 p.
3. Chopra S, Davies EL. Breast cancer. Med (United Kingdom) [Internet]. 2020;48(2):113–8. Available from: https://doi.org/10.1016/j.mpmed.2019.11.009
4. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol. 2008;9(8):730–56.
5. Perou CM, Sørile T, Eisen MB, Van De Rijn M, Jeffrey SS, Ress CA, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747–52.
6. Curtis C, Shah SP, Chin SF, Turashvili G, Rueda OM, Dunning MJ, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature. 2012;486(7403):346–52.
7. Angahar LT. An Overview of Breast Cancer Epidemiology, Risk Factors, Pathophysiology, and Cancer Risks Reduction. MOJ Biol Med. 2017;1(4):92–6.
8. Reynolds P. Smoking and breast cancer. J Mammary Gland Biol Neoplasia. 2013;18(1):15–23.
9. South African National Cancer Registry. Cancer in South Africa (2017). WwwNcrAcZa [Internet]. 2017;1. Available from: http://www.cansa.org.za/south-african-cancer-statistics/
10. Fregene A, Lisa A, Newman MPH, Newman LA. Breast Cancer in Sub-Saharan Africa: How Does It Relate to Breast Cancer in African-American Women? 2005; Available from: www.interscience.wiley.com
11. Groenewald P, Bradshaw D, Daniels J, Matzopoulos R, Bourne D, Blease D, et al. Cause of death and premature mortality in Suggested citation Acknowledgements Copies of the report [Internet]. 2001. 2001–

2006 p. Available from: www.mrc.ac.za/bod.bod.htm%5Cnwww.capetown.gov.za/health%5Cnwww.capegateway.gov.za/health
12. Bedoya AM, Arcila AL, Cardona-Arias JA. Risk factors for breast cancer. Rev Cuba Obstet y Ginecol. 2019;45(2).
13. Djuric Z, Depper JB, Uhley V, Smith D, Lababidi S, Martino S, et al. Oxidative DNA damage levels in blood from women at high risk for breast cancer are associated with dietary intakes of meats, vegetables, and fruits. Vol. 98, Journal of the American Dietetic Association. 1998. p. 524–8.
14. Hoffman M, de Pinho H, Cooper D, Sayed R, Dent DM, Gudgeon A, et al. Breast cancer incidence and determinants of cancer stage in the Western Cape. S Afr J Obstet Gynaecol. 2001;7(1).
15. Breast cancer awareness | Western Cape Government [Internet]. [cited 2021 Jul 31]. Available from: https://www.westerncape.gov.za/general-publication/breast-cancer-awareness
16. Schoeman M, Apffelstaedt JP, Baatjes K, Urban M. Implementation of a breast cancer genetic service in South Africa - Lessons learned. South African Med J. 2013;103(8):529–33.
17. Dansey RD, Hessel PA, Browde S, Lange M, Derman D, Nissenbaum M, et al. Lack of a significant independent effect of race on survival in breast cancer. Cancer. 1988;61(9).
18. Moodley J, Constant D, Mwaka AD, Scott SE, Walter FM. Mapping awareness of breast and cervical cancer risk factors, symptoms and lay beliefs in Uganda and South Africa. PLoS One [Internet]. 2020;15(10 October):1–17. Available from: http://dx.doi.org/10.1371/journal.pone.0240788
19. Radecka B, Litwiniuk M. Breast cancer in young women. Ginekol Pol. 2016;87(9):659–63.
20. Eugênio DSG, Souza JA, Chojniak R, Bitencourt AGV, Graziano L, Souza EF. Breast cancer features in women under the age of 40 years. Rev Assoc Med Bras. 2016;62(8):755–61.
21. Emiroglu M, Karaali C, Sert I, Salimoglu S, Ugurlu L, Aksoy S, et al. Comparison of Clinical and Pathological Differences of Breast Cancer

Patients under 35 and above 55 Years of Age. J Breast Heal. 2015;11(3):123–7.
22. Silvera SAN, Rohan TE. Benign proliferative epithelial disorders of the breast: A review of the epidemiologic evidence. Breast Cancer Res Treat. 2008;110(3):397–409.
23. Friedenreich CM, Bryant HE, Alexander F, Hugh J, Danyluk J, Page DL. Risk factors for benign proliferative breast disease. Int J Epidemiol. 2000;29(4):637–44.
24. Mastalgia: a review of management. [Internet]. [cited 2021 Aug 25]. Available from: https://reference.medscape.com/medline/abstract/16444894
25. Griffith CDM, Dowle CS, Hinton CP, Blarney RW. The breast pain clinic: A rational approach to classification and treatment of breast pain. Postgrad Med J. 1987;63(741):547–9.
26. Sivarajah R, Welkie J, Mack J, Casas RS, Paulishak M, Chetlen AL. A review of breast pain: Causes, imaging recommendations, and treatment. J Breast Imaging. 2020;2(1):101–11.
27. Mohallem Fonseca M, Lamb LR, Verma R, Ogunkinle O, Seely JM. Breast pain and cancer: should we continue to work-up isolated breast pain? Breast Cancer Res Treat [Internet]. 2019;177(3):619–27. Available from: https://doi.org/10.1007/s10549-019-05354-1
28. Holbrook AI, Moy L, Akin EA, Baron P, Didwania AD, Heller SL, et al. ACR Appropriateness Criteria ® Breast Pain. J Am Coll Radiol [Internet]. 2018;15(11):S276–82. Available from: https://doi.org/10.1016/j.jacr.2018.09.014
29. Harris V, Jackson V. Indications for Breast Imaging in Women under Age 35 Years. RSNA. 1989;445–8.
30. Moy L, Heller SL, Bailey L, D'Orsi C, DiFlorio RM, Green ED, et al. ACR Appropriateness Criteria® Palpable Breast Masses. J Am Coll Radiol [Internet]. 2017;14(5):S203–24. Available from: http://dx.doi.org/10.1016/j.jacr.2017.02.033
31. Carney PA, Miglioretti DL, Yankaskas BC, Kerlikowske K, Rosenberg R, Rutter CM. Erratum: Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of

screening mammography (Annals of Internal Medicine (2003) 138 (168-175)). Ann Intern Med. 2003;138(9):771.

32. WESTERN CAPE [Internet]. [cited 2021 Jul 31]. Available from: https://apps.statssa.gov.za/census01/Census96/HTML/press/Part017.html

33. Harvey JA, Mahoney MC, Newell MS, Bailey L, Barke LD, Orsi CD, et al. ACR Appropriateness Criteria Palpable Breast Masses. JACR [Internet]. 2013;10(10):742-749.e3. Available from: http://dx.doi.org/10.1016/j.jacr.2013.06.013

34. Gundry KR. Breast ultrasound: Indications and findings. Clin Obstet Gynecol. 2016;59(2):380–93.

35. Loving VA, DeMartini WB, Eby PR, Gutierrez RL, Peacock S, Lehman CD. Targeted ultrasound in women younger than 30 years with focal breast signs or symptoms: Outcomes analyses and management implications. Am J Roentgenol. 2010;195(6):1472–7.

36. Fraker JL, Clune CG, Sahni SK, Yaganti A, Vegunta S. Prevalence , Impact , and Diagnostic Challenges of Benign Breast Disease : A Narrative Review. 2023;(May):765–78.

37. Orr B, Kelley JL. Benign Breast Diseases: Evaluation and Management. Clin Obstet Gynecol. 2016;59(4).

38. Bartow SA, Pathak DR, Black WC, Key CR, Teaf SR. Prevalence of benign, atypical, and malignant breast lesions in populations at different risk for breast cancer. A forensic autopsy study. Cancer. 1987;60(11):2751–60.

39. Cole P, Elwood JM, Kaplan SD. Incidence rates and risk factors of benign breast neoplasms. Am J Epidemiol. 1978;108(2).

40. Park YM, Kim EK, Lee JH, Ryu JH, Han SS, Choi SJ, et al. Palpable breast masses with probably benign morphology at sonography: Can biopsy be deferred? Acta radiol. 2008;49(10).

41. Raza S, Chikarmane SA, Neilsen SS, Zorn LM, Birdwell RL. BI-RADS 3, 4, and 5 lesions: Value of US in management - Follow-up and outcome. Radiology. 2008;248(3).

42. Graf O, Helbich TH, Fuchsjaeger MH, Hopf G, Morgun M, Graf C, et al. Follow-up of palpable circumscribed noncalcified solid breast masses at

mammography and US: can biopsy be averted? Radiology. 2004;233(3):850–6.

43. Graf O, Helbich TH, Hopf G, Graf C, Sickles EA. at US : Is Follow-up an Acceptable Alternative to Biopsy ? 1 Methods : Results : Conclusion : Radiology. 2007;244(1).

44. Harvey JA, Nicholson BT, LoRusso AP, Cohen MA, Bovbjerg VE. Short-term follow-up of palpable breast lesions with benign imaging features: Evaluation of 375 lesions in 320 women. Am J Roentgenol. 2009;193(6):1723–30.

Appendix A - South African Journal of Radiology Instructions to Authors

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters

(including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of six paragraphs labelled Background, Objectives, Method, Results, Conclusion and Contribution.

- Background: *Why do we care about the problem?* State the context and purpose of the study. (What practical, scientific or theoretical gap is your research filling?)
- Objectives: *What problem are you trying to solve*? What is the scope of your work (e.g. is it a generalised approach or for a specific situation)? Be careful not to use too much jargon.
- Method: *How did you go about solving or making progress on the problem*? State how the study was performed and which statistical tests were used. (What did you actually do to get the results?) Clearly express the basic design of the study; name or briefly describe the basic methodology used without going into excessive detail. Be sure to indicate the key techniques used.
- Results: *What is the answer*? Present the main findings (that is, as a result of completing the procedure or study, state what you have learnt, invented or created). Identify trends, relative changes or differences in answers to questions.
- Conclusion: *What are the implications of your answer*? Briefly summarise any potential implications. (What are the larger implications of your findings, especially for the problem or gap identified in your motivation?)
- Contribution: What key insights into the research results and its future function are revealed? How do these insights link to the focus and scope of the journal? It should be a concise statement of the primary contribution of the manuscript; and how it fits within the scope of the journal.
  Do not cite references and do not use abbreviations excessively in the abstract.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by the use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic and should clarify the knowledge gap that this study will address. Your argument should be supported by the use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design: This must address the following:

- Study design: An outline of the type of study design.
- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used or steps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution’s name and permit numbers should be stated here.

Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the SI convention and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

- **Competing interests**: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our policy on competing interests.
- **Author contributions:** All authors must meet the criteria for authorship as outlined in the authorship policy and author contribution statement policies.
- **Funding:** Provide information on funding if relevant
- **Data availability:** All research articles are encouraged to have a data availability statement.
- **Disclaimer:** A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.

Appendix B- Ethical approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

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13 June 2022

HREC REF: 333/2022

Dr R Gamieldien
Diagnostic Radiology
C-Floor, C16 NGSH
Email: Rufkah.gamieldien@uct.ac.za

Dear Dr Gamieldien

PROJECT TITLE: **BREAST ULTRASOUND IN FEMALES 35 YEARS OLD AND BELOW AT A TERTIARY REFERRAL ACADEMIC CENTER IN CAPE TOWN, SOUTH AFRICA: INDICATIONS AND OUTCOMES ANALYSIS, A RETROSPECTIVE QUANTITATIVE STUDY**

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19. Please refer to guidance letter dated 02 February 2022 on our website: http://www.health.uct.ac.za/fhs/research/humanethics/forms

Approval is granted for one year until the 30 June 2023.

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF 333/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

HREC/ref 333.2022

Appendix C- Ethics approval renewal

HUMAN RESEARCH
ETHICS COMMITTEE

- 3 JUL 2023

HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) **This serves as notification of annual approval, including any documentation described below.**			
☑ Approved	Annual progress report	Approved until/next renewal date	30.06.2024
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	3/7/2023

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC

Principal Investigator to complete the following

1. Protocol information

Date (when submitting this form)	29/06/2023		
HREC REF Number	333/2022	Current Ethics Approval was granted until	30 June 2023
Protocol title	Breast ultrasound in females 35 years old and below at a tertiary referral academic center in Cape Town, South Africa: indications and outcomes analysis, a retrospective quantitative study.		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes	☑ No	
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)